Gynecologic Oncology **81,** 216–224 (2001)
doi:10.1006/gyno.2001.6121, available online at http://www.idealibrary.com on IDEAL®

Repetitive High-Dose Topotecan, Carboplatin, and Paclitaxel with Peripheral Blood Progenitor Cell Support in Previously Untreated Ovarian Cancer: Results of a Phase I Study

H. Miles Prince,* Danny Rischin,*,† Michael Quinn,† David Allen,† Robert Planner,† Deborah Neesham,† Priscilla Gates,* and Jill Davison*

**Blood and Marrow Transplant Service, Division of Haematology and Medical Oncology, Peter MacCallum Cancer Institute, Melbourne 3000; Victoria; and †Melbourne Centre for Gynaecologic Cancer Trials, affiliates: Peter MacCallum Cancer Institute, Royal Women's Hospital, Mercy Hospital for Women, Melbourne, Australia*

Received July 6, 2000; published online April 4, 2001

Objective. **In view of the significant activity of topotecan in ovarian cancer with dose-limiting toxicity (DLT) of myelosuppression, we evaluated the addition of topotecan to carboplatin and paclitaxel with peripheral blood progenitor cell (PBPC) support.**

Methods. **Patients with previously untreated stage IIIC or IV ovarian cancer with macroscopic residual disease following primary debulking surgery were eligible. Patients received two cycles of carboplatin AUC = 5 and 175 mg/m^2 of paclitaxel with collection of PBPCs after the second cycle. Patients subsequently received three cycles of high-dose therapy (HDT) with topotecan on a daily ×5 schedule, paclitaxel (250 mg/m^2 over 24 h), and carboplatin (AUC = 12–16).**

Results. **Nineteen patients with a median age of 49 years (range 21–63) were enrolled and topotecan was escalated in 6 patient cohorts up to a dose of 4.5 mg/m^2/day. Fifty-two of the planned 57 treatment cycles were delivered with no treatment-related deaths. Neutrophil and platelet recovery was rapid and the interval between HDT was 28 days. Febrile neutropenia occurred following 57% of all HDT cycles. DLTs of mucositis and diarrhea were observed at topotecan (4.5 mg/m^2/day), paclitaxel (250 mg/m^2) and carboplatin (AUC = 12). The protocol was subsequently modified to administer topotecan (2.5 mg/m^2/day) with carboplatin (AUC = 16); however, 2 patients developed grade 4 diarrhea (1 with grade 3 mucositis and 1 with grade 4 mucositis). The clinical CR rate was 73% (14/19) with an overall clinical response rate of 95% (18/19). Of the 14 patients with a CCR, 13 of these underwent a second-look laparotomy with 8 (61%) achieving a pthological CR. With a median follow-up of 28 months (range 11–40 months), the median PFS is 36 months and OS has not been reached.**

Conclusion. **When combined with carboplatin (AUC = 12) and paclitaxel (250 mg/m^2), the recommended topotecan dose is 3.5 mg/m^2/day for 5 days. This outpatient HDT regimen combines three of the most active drugs in ovarian cancer with acceptable toxicity and promising activity.** © 2001 Academic Press

Key Words: **ovarian cancer; high-dose therapy; topotecan; paclitaxel; carboplatin.**

INTRODUCTION

The most effective front-line regimen to date for patients with suboptimally debulked stage III or IV ovarian cancer is a combination of a platinum and paclitaxel [1]. Although the response rate is high, a substantial number of patients do not achieve remission and the majority of patients ultimately relapse from their disease. Consequently, alternative therapeutic strategies warrant investigation to further improve the outcome of such patients.

Topotecan has substantial activity in ovarian cancer [2, 3] and, more recently, investigators have attempted to combine paclitaxel, cisplatin/carboplatin, and topotecan. However, combining these three drugs has been problematic because of dose-limiting toxicities (DLT) of neutropenia and thrombocytopenia which have required relative dose reductions of the individual agents [4–18]. These relative dose reductions may have an adverse effect on outcome [19]. One way of overcoming these hemopoietic toxicities is to support the therapy with peripheral blood progenitor cells (PBPCs). Furthermore, the use of PBPCs has the potential not only to escalate the drugs beyond the conventional-dose range, but also to allow the administration of repeated cycles of high-dose therapy (HDT) in rapid succession [20–26].

Although there is both *in vitro* and *in vivo* evidence for a dose–response relationship within the conventional-dose range for cisplatin in ovarian cancer, the evidence for carboplatin is less convincing and the benefit of dose-escalating platinum agents beyond the conventional-dose range remains unproven [27–34]. Nonetheless, the side-effect profile of carboplatin allows dose escalation to be explored with the support of PBPCs. There is evidence of a dose–response relationship with paclitaxel within the conventional-dose range, although this seems to have a limited impact on overall survival [35]. There is little information about the dose–response relationship of topotecan in ovarian cancer; however, one rationale for the

0090-8258/01 $35.00

dose escalation of topotecan is to overcome low-level resistance to topotecan conferred by P-glycoprotein overexpression in ovarian cancer cells which has been demonstrated in experimental models [36, 37]. Consequently, one objective in this study was not to focus on dramatically dose escalating the agents but to combine these three drugs while at least maintaining the dose intensity of individual agents.

The predominant nonhemopoietic DLT of carboplatin is renal toxicity and ototoxicity, observed usually at predicted AUC doses of above 20 mg/ml · min [20–24], while the major nonhemopoietic DLT for paclitaxel is neurological [25, 38]. In phase I trials, the DLT of single-agent topotecan given with G-CSF has been neutropenia and thrombocytopenia, with the recommended dose as a single agent being 1.5 mg/m^2/day for 5 days every 3 weeks [39, 40]. Taken together, these three drugs appear to be very suitable candidates for examining dose-escalation strategies.

In this trial we sought to examine the feasibility of combining carboplatin, paclitaxel, and topotecan with PBPC support in previously untreated patients with ovarian cancer and to determine a suitable dose for subsequent studies. Specifically, we aimed to develop an intensive regimen where patients could be managed largely as outpatients.

METHODS

The primary objective of this study was to determine the safety and maximum tolerated doses (MTD) of this drug combination, with the secondary objectives being efficacy of this combination therapy as measured by clinical complete remission (CCR) rates, pathological CR rates (pCR), partial remission (PR) rates, overall (OS), and progression-free survival (PFS).

Eligibility Criteria

Patients between 18 and 65 years were eligible if they had histologically proven stage IIIC or IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma which was either suboptimally debulked or optimally debulked (<1 cm) with macroscopically visible residual disease. Patients with clear cell histology were not required to have macroscopically visible disease. Patients were required to have an ECOG performance status <3, life expectancy of at least 2 months, adequate bone marrow function with an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L, adequate liver function with bilirubin upper limit of normal and aspartate transaminase ≤2 times upper limit of normal, adequate renal function with serum urea and creatinine ≤1.5× upper limit of normal, and glomerular filtration rate (GFR) of ≥60 ml/min. The study was approved by the ethics committee of the Peter MacCallum Cancer Institute and all patients provided written informed consent.

Disease Assessment Prior to Treatment

Following initial surgery, disease was assessed by CA125, chest X ray, and chest/abdominal/pelvic CT scan.

Conventional-Dose Chemotherapy and PBPC Mobilization

All patients had GFR (Tc^{99m} DTPA clearance) [41] determined at study entry and prior to each cycle of high-dose therapy. Carboplatin was administered according to a targeted AUC and calculated using the Calvert formula [42]. The first cycle of conventional-dose chemotherapy was administered according to the following schedule: paclitaxel (Anzatax; FH Faulding Pharmaceuticals, Adelaide, Australia), 175 mg/m^2 as a 24-h infusion on day 1. Premedication consisted of dexamethasone 20 mg po 12 and 6 h prior to the commencement of infusion, 25 mg iv promethazine, and 50 mg iv ranitidine over 15 min commencing 30 min prior to infusion. On day 2, carboplatin (AUC = 5 mg/ml · min) was administered as a 1-h infusion. G-CSF (lenograstim; Amrad Pharmaceuticals Pty. Ltd., Melbourne, Australia) (263 μg) was administered subcutaneously daily from day 3 until ANC $>1.5 \times 10^9$/L for 3 consecutive days or $>5 \times 10^9$/L. Twenty-one days following the first cycle, patients received a further cycle of the same chemotherapy and, for the purpose of mobilizing PBPC, received 10 μg/kg G-CSF subcutaneously daily up to, but not including, the last day of PBPC collection.

Apheresis

Apheresis and cell processing were performed as previously described [43]. Briefly, apheresis was initiated when ANC $\geq 1.0 \times 10^9$/L and peripheral blood $CD34^+$ cells $\geq 5 \times 10^6$/L. A minimum of 7 L of blood was processed with each apheresis. Apheresis was continued until sufficient cells were collected to support three separate cycles of intensive therapy, i.e., $\geq 1 \times 10^6$/kg 34^+ cells infused following *each* cycle of intensive therapy. If the CD34 count was borderline (i.e., $0.5–1.0 \times 10^6$/kg), the autograft was considered adequate if colony-forming units granulocyte–macrophage (CFU-GM) exceeded 10×10^4/kg/infusion. To achieve uniformity, each day's collection was divided into three separate bags; thus each reinfusion contained PBPC collected from each day of collection. A repeat collection was performed if the initial set of collections was deemed inadequate (CD34 cells for each infusion $<1.0 \times 10^6$/kg and CFU-GM $<10 \times 10^4$/kg). PBPCs were cryopreserved with 10% DMSO with controlled-rate freezing and stored in vapor phase liquid nitrogen.

High-Dose Therapy

Six cohorts of four patients were planned. A minimum of two patients were required to complete HDT (all three cycles) in the absence of demonstrable DLT before any patient received therapy at the next dose level.

In all cohorts, 250 mg/m^2 of paclitaxel was administered as

TABLE 1
High-Dose Therapy Regimen (×3) Every 28 Days

	Dose	d-6	d-5	d-4	d-3	d-2	d-1	d0	d+1→
Paclitaxel	250 mg/m^2			CI					
Carboplatin	Escalating	(CI)[a]			CI				
Topotecan	Escalating	X	X	X	X	X			
PBPC								X	
G-CSF	263 μg/day								X

Note. CI, continuous infusion; PBPC, peripheral blood progenitor cells.
[a] Selected patients in cohort 6 (see text).

24-h infusion commencing on day (−4) (Table 1). For cohorts 1–5, carboplatin (AUC = 12 mg/ml · min) was administered as a continuous infusion over 24 h on day (−3) following the completion of paclitaxel. In view of reports of synergy and a pharmacokinetic interaction, when topotecan is given after platinum agents [4, 44–46], patients in cohort 6 received carboplatin (AUC = 16 mg/ml · min) on either day (−3) or day (−6). Patients 1 and 3 in cohort 6 received carboplatin on day (−3) with the first cycle and on day (−6) with the second cycle. Patients 2 and 4 in cohort 6 received carboplatin on day (−6) with the first cycle and day (−3) with the second cycle. If there was no significant difference in toxicity in an individual patient (patients 1–4 in cohort 6), the patient received carboplatin on day (−6) for their third cycle. For cohorts 2–6, topotecan (Hycamtin; SmithKline Beecham (Australia) Pty. Ltd., Australia) was administered over 30 min on days (−6), (−5), (−4), (−3), and (−2). Cohort 2 received 1.5 mg/m^2/day of topotecan and this was increased by 1 mg/m^2/day with each successive cohort to a maximum of 4.5 mg/m^2/day (planned for cohorts 5 and 6). The planned cycle frequency of HDT was 28 days. Frequency up to 42 days (6 weeks) was acceptable. PBPC were infused on day (0). G-CSF (263 μg sc) commenced 24 h after PBPC infusion day (+1), continuing until ANC $\geq 1.5 \times 10^9$/L for 2 consecutive days. All patients received prophylactic ciprofloxacin and acyclovir (if HSV serology positive).

Dose Adjustments and Dose-Limiting Toxicities

The anticipated duration between chemotherapy cycles was 28 days. Subsequent cycles were delayed by 7 days if day-28 blood counts did not achieve ANC $\geq 1.5 \times 10^9$/and/or platelets $\geq 100 \times 10^9$/L. Of note, we aimed to develop an intensive regimen where patients could be managed largely as outpatients; thus mucositis requiring parenteral nutrition, parenteral opiate analgesia, and inpatient fluid and electrolyte support were considered DLTs (grade 4). Similarly, diarrhea that required inpatient admission was considered a DLT (grade 4). Subsequent cycles were delayed by 7 days if reversible NCI grade 1–4 nonhematological toxicity persisted or ECOG performance status was ≥2.

Dose-limiting toxicities were defined as at least one of the following: NCI grade 4 nonhematological toxicity, inability to receive a subsequent cycle of therapy because of haematological toxicity, grade 3 neurological toxicity, cardiac toxicity, or renal toxicity, and/or withdrawal from HDT because of combined or cumulative toxicity. The MTD of HDT was defined as one dose level below the dose that induced a DLT ≥2/4 patients.

Response Assessment and Statistical Considerations

Tumor assessment was performed prior to conventional-dose therapy and HDT and after completion of HDT. This assessment included chest X ray and chest/abdomen/pelvis CT and CA125. A second-look laparotomy/laparoscopy was planned in all patients with a normal CA125 and CT scans after completion of HDT. In patients with absence of visible disease, up to 40 random biopsies were performed. Follow-up and disease reassessment were subsequently performed every 3 months with clinical examination and CA125.

Clinical complete remission was defined as the disappearance of all clinical evidence of disease and pathological complete remission as no histological evidence of disease at second-look laparotomy/laparoscpy. Partial response was defined as at least a 50% reduction in the size of all measurable tumor areas. Stable disease was defined as a patient's status failing to qualify for either a PR or progressive disease. Disease progression was defined as the appearance of a new lesion, or an increase of 25% in the sum of areas of lesions, or a 50% increase in CA125. Overall survival was determined from the time of enrollment to death from any cause and progression-free survival was defined as the time to recurrence, progression, or death from any cause.

To compare ANC and platelet recovery between the three cycles of high-dose therapy (individual patient data sets), repeated-measures ANOVA was used. Kaplan–Meier estimates of time to platelet and ANC recovery were performed and recovery with consecutive cycles was compared using the log-rank test. All results are expressed as two-sided *P* values. Statistical analysis was performed using GraphPad Prism Ver 2.01 and GraphPad StatMate Ver 1.00 for Windows 3.1 (GraphPad Software Inc., San Diego, CA).

RESULTS

Patient Characteristics

Nineteen patients with a median age of 49 years (range 21–63) were enrolled. Patient characteristics are summarized in Table 2. All patients had epithelial ovarian cancer. No patients had received prior chemotherapy for ovarian cancer, but 1 patient had previously received adjuvant chemotherapy for early stage breast cancer.

Apheresis Collections

All patients enrolled in the study obtained sufficient PBPCs to proceed to HDT. Seven patients required a second mobili-

TABLE 2
Patient Characteristics ($n = 19$)

Characteristic	*n*
Histology	
Serous papillary	13
Clear cell	4
Endometroid	2
Stage	
IIIC	16
IV	3
Residual disease following initial surgery	
<1 cm	9
1–2 cm	3
2–5 cm	5
>5 cm	2

zation and collection to achieve the target autograft yield. A median of 3 days' collection was required (range 2–8 days) with a median total collected PBPC CD34 of 7.7×10^6/kg (range 1.7–15.4). The median autograft $CD34^+$ content (to support each cycle of HDT) was 2.6×10^6/kg (range 0.6–5.2). The median number of CFU-GM infused per cycle was 11×10^4/kg (2–50) with median mononuclear cells infused per cycle of 4.1×10^8/kg (range 1.1–10.1).

Dose Intensity and Nonhemopoietic Toxicity

For the 19 patients, 52 of the planned 57 treatment cycles were delivered. Sixteen patients completed all 3 cycles, 1 completed only 2 cycles, and 2 completed only 1 cycle. There were no treatment-related deaths. As rapid hematopoietic recovery was observed after most cycles (see below), the subsequent cycle of HDT was delivered at a median of 22 days (range 17–43 days) following infusion of the PBPCs, i.e., median of 28 days between cycles of chemotherapy.

The actual doses delivered in successive cohorts and the DLTs are detailed in Table 3. No patient in cohort 1 had grade 3 or 4 toxicity. In cohort 2, two patients developed grade 3 diarrhea. In cohort 3 one patient developed grade 3 mucositis. In cohort 4, grade 3 mucositis was observed in all patients, with no grade 4 mucositis observed. One patient developed grade 3 diarrhea and one developed grade 4 diarrhea.

Grade 4 mucositis and grade 3 diarrhea were observed in the first patient (cycle 1) in cohort 5 and the toxicity was felt to be too excessive and the cohort was abandoned. The protocol was subsequently modified to test whether administering the same dose of topotecan as cohort 3 (i.e., 2.5 mg/m^2/day) with a higher dose of carboplatin (AUC = 16 mg/ml · min) was feasible. In this cohort (cohort 6), one patient developed grade 4 diarrhea and mucositis and one experienced grade 4 diarrhea and grade 3 mucositis. These two patients were withdrawn from the treatment (one patient after cycle 1 and one patient after cycle 2) because of toxicity. There was no observable difference in toxicities between patients on cohort 6 receiving carboplatin on either day (−3) or day (−6). Other toxicities (grade 1 or 2) included elevation of transaminases ($n = 7$ patients, grade 2) and neuropathy ($n = 7$ patients, grade 1). No renal impairment or ototoxicity was observed in any patient. Consequently, the MTD was defined as paclitaxel (250 mg/m^2), carboplatin (AUC = 12 mg/ml · min), and topotecan (3.5 mg/m^2/day for 5 days).

Hematological Toxicity and Recovery

Hematological recovery is detailed in Fig. 1. For all 52 HDT cycles, the median time to ANC $>1.0 \times 10^9$/L was 10 days (range 5–15) with no slowing of neutrophil recovery over consecutive cycles ($P = 0.10$; log-rank test). G-CSF was required for a median of 10 days (range 8–13 days) for each cycle of HDT. Febrile neutropenia occurred following 57% (30/52) of all HDT cycles and, when it occurred, lasted for a median of 3 days (range 1–3 days) with a median duration of systemic antibiotics of 5 days (range 1–20 days). Admission to the hospital was required following 57% (30/52) of HDT

TABLE 3
Nonhematologic Toxicity

Cohort	Patients	Cycles	Paclitaxel (mg/m^2/cycle)	Carboplatin (AUC/cycle)	Topotecan (mg/m^2/day/cycle)	Pts not completing HDT (cycles completed)	Pts with DLT/total	Grade 3 nonhematologic toxicity (pts/total cycles)	Grade 4 nonhematologic toxicity (pts/total cycles)
1	3	9	250	12	—	0	0/3	0	0
2	4	12	250	12	1.5	0	0/4	Diarrhea (2/3)	0
3	3	9	250	12	2.5	0	0/3	Mucositis (1/2)	0
4	4	12	250	12	3.5	0	1/4	Mucositis (4/7) Diarrhea (1/1)	Diarrhea (1/1)
5	1	1	250	12	4.5	1 (1)	1/1	Diarrhea (1/1)	Mucositis (1/1)
6	4	9	250	16	2.5[a]	2 (1&2)	2/4	Mucositis (1/3)	Mucositis (1/2) Diarrhea (2/2)

[a] Protocol modified with reduction of topotecan from 4.5 mg/m^2/day.

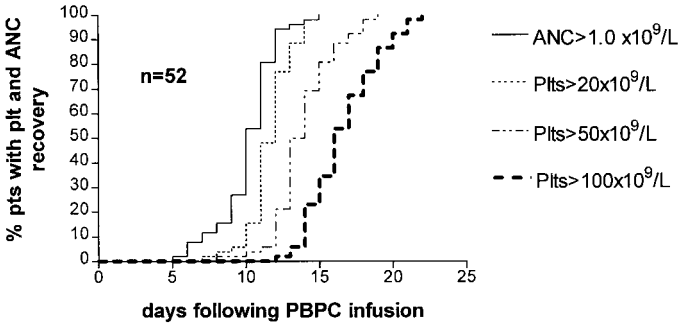

FIG. 1. Kaplan–Meier estimates of absolute neutrophil count (ANC) recovery to $>1.0 \times 10^9$/L and platelet recovery to $>20 \times 10^9$/L, $>50 \times 10^9$/L, and $>100 \times 10^9$/L.

cycles with a median inpatient stay of 7 days (range 1–48 days); the reason for admission into the hospital was febrile neutropenia (93% of cases), mucositis (3%), and diarrhea (3%).

The median time to platelet recovery $>20 \times 10^9$/L, 50×10^9/L, and 100×10^9/L was 12 (range 7–15), 14 (range 8–19), and 16 days (range 12–22), respectively. Platelet recovery was analyzed across the treatment cycles and there was no difference in recovery to 20×10^9/L ($P = 0.64$; log-rank test), 50×10^9/L ($P = 0.09$), or 100×10^9/L ($P = 0.18$) across the three consecutive cycles. There was also no difference in platelet recovery between the different cohorts ($P = 0.36$ for platelets $>100 \times 10^9$/L). A median of two platelet transfusions (range 0–6) and three packed red blood cell transfusions (range 0–7) were required following each cycle of treatment. There were 11 episodes of grade 1 or 2 bleeding.

Responses and Survival

For all 19 patients the clinical CR rate was 73% (14/19) with an overall clinical response rate of 95% (18/19). The remaining patient had SD. Sixteen patients underwent a second-look laparotomy or laparoscopy. Of the remaining 3 patients who did not undergo a second-look procedure, 1 had progressive disease, 1 had a PR with a persistently elevated CA125, and 1 had a normal CA125 and declined surgery. Of the 16 patients who had a second-look laparotomy, 8 (50%) had a pathological CR and 7 (44%) had a pathological PR (microscopic disease = 6, macroscopic disease = 1). The remaining patient had SD. Of the 14 patients with a CCR, 13 of these underwent a second-look procedure with 8 (61%) having achieved pCR. Response rates according to outcome of primary debulking procedure (i.e., prechemotherapy) are detailed in Table 4. With a median follow-up of 28 months for all alive patients (range 11–40 months), the median PFS is 36 months and OS has not been reached (Fig. 2).

TABLE 4
Responses According to Primary Debulking Procedure

Debulking result (cm)[a]	Clinical response				Pathological response			
	n	CR[b]	PR	SD	Evaluable	pCR	pPR	pSD
Stage IIIC/IV ($n = 19$)								
<1	9	8	0	1	8[c]	6	2	0
1–5	8	5	3	0	6[d]	2	3	1
>5	2	1	1	0	2	0	2	0
Stage IV	3	2	1	0	3	1	2	0

[a] All patients had disease macroscopically visible after initial surgery.
[b] All patients had elevated CA125 prior to therapy so all were evaluable for clinical response.
[c] One patient with SD did not undergo second-look laparotomy.
[d] Two patients did not have second-look laparotomy, one patient in clinical CR and one patient in clinical PR.

DISCUSSION

The role of HDT with autologous bone marrow or PBPC rescue for ovarian cancer has to date mainly focused on patients with relapsed disease or those with persistent disease following front-line therapy, with the outcome very dependent on tumor size and platinum sensitivity. The most common HDT conditioning regimens have used alkylating agents (cyclophosphamide, melphalan, thiotepa), etoposide, mitoxantrone, and carboplatin/cisplatin [47–52].

We examined an alternative approach, namely to determine whether the three of the most active agents in ovarian cancer, carboplatin, paclitaxel, and topotecan, could be combined and dose escalated as front-line therapy in patients with poor-prognosis stage III/IV disease.

Previous investigators have demonstrated that combining these drugs without PBPC support is problematic because of the combined hematological toxicity and the consequent need for relative dose reductions of the individual drugs. Indeed, severe myelotoxicity is observed in lung cancer patients when paclitaxel (135 mg/m^2 over 3 h) is combined with topotecan at doses of 1.0–1.5 mg/m^2/day$_{1-5}$ [9, 10]. With G-CSF support, 24-h infusional paclitaxel (135 mg/m^2) can be administered with 0.75 mg/m^2/day$_{1-5}$ of topotecan, with higher doses resulting in prolonged thrombocytopenia [8].

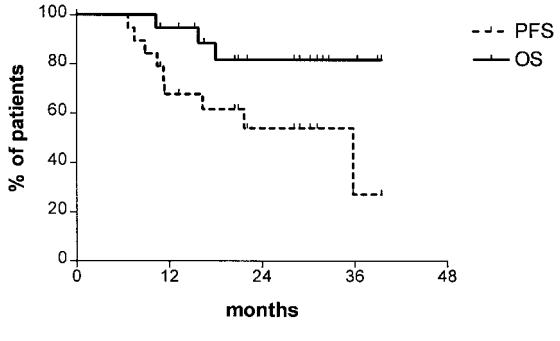

FIG. 2. Kaplan–Meier estimates of survival (OS) and progression-free survival (PFS).

Topotecan (0.75 mg/m^2/day$_{1–5}$) combined with cisplatin (75 mg/m^2/day$_1$) results in severe and prolonged neutropenia [5] and although topotecan (0.75 mg/m^2/day$_{2–6}$) can be combined with cisplatin (50 mg/m^2/day$_1$) with G-CSF support [4], higher doses result in dose-limiting thrombocytopenia. The problematic thrombocytopenia even at relatively low doses of topotecan has been confirmed by other investigators, even when using alternative dosing schedules [6, 14, 15]. Futhermore, when combined with carboplatin (AUC = 4–5 mg/ml · min), topotecan (0.75 mg/m^2/day$_{1–5}$) results in unacceptable hemopoietic toxicity even with G-CSF support [16]. Similarly, when carboplatin (AUC = 5 mg/ml · min) is combined with 3-day infusional topotecan, a total dose of 4.5 mg/m^2 can be administered; however, there is a 25% incidence of grade 3 thrombocytopenia [17].

Herben *et al.* recently demonstrated that when the three agents are combined, the MTD with G-CSF support is paclitaxel (110 mg/m^2 over 24 h), cisplatin (75 mg/m^2), and topotecan (0.3 mg/m^2/day for 5 days) [53]. Carboplatin, paclitaxel, and topotecan have been combined in two reported trials without PBPC support. Hainsworth *et al.* found that the recommended doses were carboplatin (AUC 5 mg/ml · min), paclitaxel (135 mg/m^2 over 1 h), and topotecan (0.75 mg/m^2/day) for 3 days. G-CSF did not permit further dose escalation as thrombocytopenia was dose limiting [7]. Dunphy *et al.,* in a preliminary report were able to deliver carboplatin (AUC 5 mg/ml · min), paclitaxel (175 mg/m^2), and topotecan (1.0 mg/m^2/day$_{1–4}$) with G-CSF support [18].

Our results indicate that by utilizing PBPCs support, all three drugs can be administered with modest dose escalation and acceptable nonhematological toxicity with an MTD of paclitaxel (250 mg/m^2), topotecan (3.5 mg/m^2/day × 5 days), and carboplatin (AUC = 12 mg/ml · min). Indeed, all patients had rapid hemopoietic recovery after each cycle and were able to complete therapy with few treatment delays. Furthermore, in this poor prognosis group of patients the remission rates, PFS, and OS results are promising.

In the earlier Phase I studies with topotecan (1.5 mg/m^2/day$_{1–5}$), the DLTs were neutropenia and thrombocytopenia and nonhaematological toxicities of vomiting, diarrhea, alopecia, fatigue, fever, asthenia and dyspnea were mild and not dose limiting [39]. Doses up to 3.5 mg/m^2/day$_{1–5}$ (total dose = 17.5 mg/m^2) could be administered with G-CSF support, with higher doses resulting in severe and prolonged thrombocytopenia. Other investigators have also demonstrated that when combined with cyclophosphamide, total topotecan doses beyond 5 mg/m^2 result in prolonged thrombocytopenia, underscoring the need for PBPC support at such doses [54]. The experience with topotecan in HDT regimens with PBPC support is limited. When combined with cyclophosphamide (3 g/m^2) and melphalan (140 mg/m^2) given as a single cycle, doses of topotecan up to 2.75 mg/m^2/day$_{1–5}$ have been administered with moderate mucositis and diarrhea [55] and preliminary results indicate that topotecan may be able to be combined with etoposide [56].

In this study we were able to increase the dose of topotecan to 3.5 mg/m^2/day for 5 days (total dose = 17.5 mg/m^2), an approximate 2.3-fold increase over the conventional dose, with the DLTs being mucositis and diarrhea. Of note, we designed this study to treat patients largely in the outpatient setting and thus, unlike most HDT studies, deemed the need for opiate analgesics or parenteral nutrition as DLTs. Our observed DLTs of mucositis and diarrhea were probably a result of the combined toxicities of the three agents, as other investigators have been able to escalate single-agent topotecan to the same dose (without PBPCs) without observing significant nonhematological toxicities [40]. An important question not addressed by our study is the MTD of topotecan alone with PBPC support.

Sequence-dependent toxicity has been observed in previous trials of cisplatin and topotecan, with increased myelosuppression when cisplatin precedes topotecan, which may be explained by a pharmacokinetic interaction with lower topotecan clearance when cisplatin precedes topotecan [4]. Furthermore, preclinical studies have suggested possible anti-tumor synergy when cisplatin precedes topotecan [44]. There has also been an preliminary report of increased myelosuppression when carboplatin is given on day 1 compared to day 5 of topotecan, but no pharmacokinetic interaction that could account for this difference could be found [46]. In a HDT regimen with PBPC support, the sequence will be important only if it results in differences in nonhematological toxicities or in efficacy. Patients in cohort 6 received one cycle with carboplatin on day 4 of topotecan and another cycle with carboplatin administered on the first day of topotecan; there was no apparent difference in toxicity, although only four patients received both sequences and this was at a dose level that resulted in unacceptable toxicity with either sequence. Hence, further work is needed to establish whether there are any sequence-dependent differences in toxicity or efficacy with this high-dose regimen. Of note, there has been no recognized sequence-dependent toxicity differences with paclitaxel and topotecan [8].

Our results demonstrate that carboplatin (AUC = 12 mg/ml · min, as determined by GFR estimated by Tc^{99m} DTPA clearance [41]) can be administered with paclitaxel (250 mg/m^2) and topotecan (17.5 mg/m^2) however, increasing the dose to AUC = 16 mg/ml · min results in unacceptable mucositis and diarrhea. The carboplatin AUC dose of 12 mg/ml · min is only a relatively modest increase over conventional-dose carboplatin, and because of the longer interval between the three cycles of HDT (28 days vs 21 days with conventional-dose carboplatin), the total delivered dose of the drug is not substantially intensified. When carboplatin is combined with paclitaxel at an AUC dose of 5 mg/ml · min, this results in an AUC dose of 1.66 mg/ml · min per week for 18 weeks and a total AUC dose of 30 mg/ml · min. In this study we were able to increase the total dose of carboplatin to an AUC of 46 mg/ml · min over the same time period. Nonetheless, although this increase in car-

boplatin is modest, it was not at the expense of the doses of topotecan or paclitaxel administered.

The MTD of carboplatin in this study was substantially lower than what can be achieved when it is dose escalated alone. Carboplatin can be escalated to an AUC dose of 7 mg/ml · min every 14 days with G-CSF [57] and, by utilizing PBPCs, doses up to and beyond AUC of 20 mg/ml · min have been achieved with DLTs of renal and ototoxicity [20–24, 26]. Of interest, these studies dosed patients according to body surface area and retrospectively calculated the carboplatin AUC, and thus the MTD of single-agent carboplatin with the use of PBPC support remains unknown. Other investigators have recently demonstrated that when combined with paclitaxel (250 mg/m^2), the MTD of carboplatin is 16 mg/ml · min with DLTs being dehydration, diarrhea, and electrolyte imbalances [58].

Schilder *et al.* are the only other investigators that have examined the feasibility of combining carboplatin, paclitaxel, and topotecan with PBPC support and, like in our study, administered three cycles of this HDT regimen. The MTD total doses were paclitaxel (250 mg/m^2), carboplatin (AUC = 16 mg/ml · min), and topotecan (12.5 mg/m^2). It is of interest that severe hemorrhagic mucositis was observed at a topotecan dose of 15 mg/m^2, which may be related to the administration of the topotecan as a 24-h infusion [59]. As the recommended single-agent dose of topotecan as a 24-h infusion without PBPC support is 8.4–12.5 mg/m^2 [60, 61], Schilder *et al.*'s recommended dose of 12.5 mg/m^2 achieves little, if any, dose escalation. Furthermore, the efficacy of this infusional topotecan schedule is questionable, with no activity seen in the phase I/II trials [60–62], and when given at a lower dose at weekly intervals it is clearly inferior to the daily time five schedule [63]. Consequently, we believe that our HDT regimen which utilizes a daily times five schedule may be preferable for phase II or III trials.

The response rate in our study was promising, with 8/16 evaluable patients achieving a pathological CR and a median PFS for all patients of 36 months. Nonetheless, the majority of pathological CRs were observed in patients with "optimally" debulked disease (<1 cm but all patients had macroscopically visible disease). Given that only 2 patients had disease >5 cm after initial surgery, no conclusions can be drawn as to the value of pursuing this strategy in such patients. Like in all HDT studies, there is selection bias in the patient population with all patients being under 65 years (also relatively low median age in this study) with a relatively good performance status at study entry. Consequently, only a randomized study would determine the benefit of this approach over conventional-dose therapy.

We conclude that topotecan, carboplatin, and paclitaxel can be combined using PBPC support to treat patients with advanced ovarian cancer. The promising results of this study warrant further exploration.

ACKNOWLEDGMENTS

The authors thank SmithKline Beecham (Australia) Pty. Ltd., FH Faulding Pharmaceuticals, Australia, and Amrad Pharmaceuticals Pty. Ltd., Australia, for their generous support of this study. We also thank the nurse coordinators, research nurses, apheresis nurses, and nursing staff on the Haematology/Oncology and Day Wards at Peter MacCallum Cancer Institute for their commitment, dedication, and expert patient care.

REFERENCES

1. McGuire WP, Hoskins WJ, Brady MF, *et al.* Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1–6.
2. Bookman MA, Malmstom H, Bolis G, *et al.* Topotecan for the treatment of advanced epithelial ovarian cancer: an open-label phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel. J Clin Oncol 1998;16:3345–52.
3. ten Bokkel Huinink W, Gore M, Carmichael J, *et al.* Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 1997;15:2183–93.
4. Rowinsky EK, Kaufmann SH, Baker SD, *et al.* Sequences of topotecan and cisplatin: a phase I, pharmacologic, and in vitro studies to examine sequence dependence. J Clin Oncol 1996;14:3074–84.
5. Raymond E, Burris HA, Rowinsky EK, *et al.* Phase I study of daily times five topotecan and single injection of cisplatin in patients with previously untreated non-small-cell lung carcinoma. Ann Oncol 1997;8:1003–8.
6. Miller AA, Hargis JB, Lilenbaum RC, *et al.* Phase I study of topotecan and cisplatin in patients with advanced solid tumours: a cancer and leukemia group B study. J Clin Oncol 1994;12:2743–50.
7. Hainsworth JD, Burris HA III, Morrissey LH, *et al.* Phase I trial of paclitaxel, carboplatin, and topotecan with or without filgrastim (granulocyte-colony stimulating factor) in the treatment of patients with advanced, refractory cancer. Cancer 1999;85:1179–85.
8. O'Reilly S, Fleming GF, Barker SD, *et al.* Phase I trial and pharmacologic trial of sequences of paclitaxel and topotecan in previously treated ovarian epithelial malignancies: a Gynecologic Oncology Group sudy. J Clin Oncol 1997;15:177–86.
9. Tweedy CR, Andrews DF, Ball T. Topotecan and paclitaxel in extensive stage small cell lung cancer as initial therapy. Proc Am Soc Clin Oncol 1999;18:525a–2025.
10. Jacobs SA, Jett JR, Belani CP, *et al.* Topotecan and paclitaxel, an active couplet, in untreated extensive disease small cell lung cancer. Proc Am Soc Clin Oncol 1999;18:470a–1814.
11. Fleming GF, Kugler JW, Hoffman PC, *et al.* Phase II trial of paclitaxel and topotecan with granulocyte colony-stimulating factor support in stage IV breast cancer. J Clin Oncol 1998;16:2032–37.
12. Lynch TJ, Herndon J, Lilenbaum RC, *et al.* Toxicity of paclitaxel and topotecan with previously untreated extensive small cell lung cancer. Proc Am Soc Clin Oncol 1999;18:515a–1987.
13. Penson RT, Supko JG, Cook SE, *et al.* A phase I/II and pharmacokinetic study of 96 hour infusional topotecan and paclitaxel chemotherapy for relapsed epithelial ovarian cancer. Proc Am Soc Clin Oncol 1999;18:382a–1477.
14. Piver SM, Ghamande SA. Role of salvage chemotherapy with topotecan and cisplatin in patients with paclitaxel and platinum resistant advanced ovarian cancer. Proc Am Soc Clin Oncol 1999;18:383a–1478.
15. Fiorica J, Grendys E, Holloway R, *et al.* Phase II trial of topotecan combined with cisplatin in squamous and non-squamous cervival cancer: preliminary results. Proc Am Soc Clin Oncol 1999;18:373a–1441.
16. Gordon AN, Doherty M, Hancock KC, *et al.* Phase I study of topotecan

with carboplatin alternating with paclitaxel via a 3 hour infusion in combination with carboplatin in treatment of newly diagnosed ovarian cancer patients. Proc Am Soc Clin Oncol 1999;18:364a–1408.

17. Bolis G, Scarfone G, Villa A, *et al.* A phase I study of carboplatin and escalating dose of topotecan in late recurrent ovarian carcinoma. Proc Am Soc Clin Oncol 1999;18:366a–1414.
18. Dunphy F, Dunleavy T, Turcotte C, *et al.* Phase I study of topotecan plus carboplatin/paclitaxel in advance solid tumours. Proc Am Soc Clin Oncol 1999;18:209a–802.
19. Cannistra SA. Back to the future: multiagent chemotherapy in ovarian cancer revisited. J Clin Oncol 1999;17:741–3.
20. Shea TC, Mason JR, Storniolo AM, *et al.* Sequential cycles of high-dose carboplatin administered with recombinant human granulocyte–macrophage colony-stimulating factor and repeated infusions of autologous peripheral-blood progenitor cells: a novel and effective method for delivering multiple courses of dose-intensive therapy. J Clin Oncol 1992;10:464–73.
21. Shea TC, Mason JR, Breslin M, *et al.* Reinfusion and serial measurements of carboplatin-mobilized peripheral-blood progenitor cell in patients receiving multiple cycles of high-dose chemotherapy. J Clin Oncol 1994; 12:1012–20.
22. Crown J, Wasserheit C, Hakes T, *et al.* Rapid delivery of multiple courses of high-dose chemotherapy with granulocyte colony-stimulating factor and peripheral blood derived hematopoietic progenitor cells. J Natl Cancer Inst 1992;84:1935–36.
23. Fennelly D, Wasserheit C, Schneider J, *et al.* Simultaneous dose-escalation and schedule intensification of carboplatin-based chemotherapy using peripheral blood progenitor cells and filgrastim: a phase I trial. Cancer Res 1994;54:6137–42.
24. Wandt H, Birkmann J, Denzel T, *et al.* Sequential cycles of high-dose chemotherapy with dose escalation of carboplatin with or without paclitaxel supported by G-CSF mobilized peripheral blood progenitor cells: a phase I/II study in advanced ovarian cancer. Bone Marrow Transplantation 1999;23:763–70.
25. Fennelly DW, Aghajanian C, Shapiro F, *et al.* Dose escalation of paclitaxel with high-dose carboplatin using peripheral blood progenitor cell support in patients with advanced ovarian cancer. Semin Oncol 1997;24: S2-26–30.
26. Aghajanian C, Fennelly D, Shapiro F, *et al.* Phase II study of "dose-dense" high-dose chemotherapy treatment with peripheral-blood progenitor-cell support as primary treatment for patients with advanced ovarian cancer. J Clin Oncol 1998;16:1852–60.
27. Herrin VE, Thigpen JT. High-dose chemotherapy in ovarian carcinaoma. Semin Oncol 1999;26:99–105.
28. Stiff PJ, McKenzie RS, Albert DS, *et al.* Phase I clinical and pharmacokinetic study of high dose mitoxantrone combined with carboplatin, cyclophosphamide and autologous bone marrow rescue: high response rate for refractory ovarian carcinoma. J Clin Oncol 1994;12:176–83.
29. Kaye SB, Lewis CR, Paul J, *et al.* Randomized study of two doses of cisplatin with cyclophosphamide in epithelial ovarian cancer. Lancet 1992;340:329–33.
30. Behrens BC, Hamilton TC, Masuda H, *et al.* Characteristics of cisdiaminedochloroplatinum (II)-resistant human ovarian cancer cell line and its evaluation in platinum analogues. Cancer Res 1987;47:414–8.
31. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. J Clin Oncol 1987;5:756–67.
32. Murphy D, Crowther D, Renninson J, *et al.* A randomised dose intensity study in ovarian carcinoma comparing chemotherapy given at four week intervals for six cycles with half dose chemotherapy given for twelve cycles. Ann Oncol 1993;4:377–83.
33. Gore M, Mainwaring P, A'Hern R, *et al.* Randomised study of dose-intensity with single agent carboplatin in patients with epithelial ovarian cancer. London Gynaecological Oncology Group. J Clin Oncol 1998;16: 2426–34.
34. Jakobsen A, Bertelson K, Andersen JE, *et al.* Dose-effect study of carboplatin in ovarian cancer: a Danish Ovarian Cancer Group Study. J Clin Oncol 1997;15:193–8.
35. Omura GA, Brady MF, Delmore JE, *et al.* A randomized trial of paclitaxel at 2 dose levels and filgrastim at 2 doses in platinum pretreated epithelial ovarian cancer: a Gynecologic Oncology Group, SWOG, NCCTG and ECOG study. Proc Am Soc Clin Oncol 1996;15:280–755.
36. Hendricks CB, Rowinsky EK, Grochow LB, *et al.* Effect of P-glycoprotein expression on accumulation and cytotoxicity of topotecan (SK&F 104864), a new camptothecin analog. Cancer Res 1992;54:2268–78.
37. Mattern MR, Hofmann GA, Polsky RM, *et al.* In vitro and in vivo effects of clinically important camptothecin analogues in multidrug resistant cells. Oncology Res 1993;5:467–74.
38. Schiller JH, Storer B, Tutsch K, *et al.* Phase I trial of 3-hour infusion of paclitaxel with or without granulocyte colony-stimulating factor in patients with advanced cancer. J Clin Oncol 1994;12:241–8.
39. Rowinsky EK, Grochow LB, Hendricks CB, *et al.* Phase I and pharmacologic study of topotecan: a novel topoisomerase 1 inhibitor. J Clin Oncol 1992;10:647–56.
40. Rowinsky EK, Grochow LB, Sartorius SE, *et al.* Phase I and pharmacologic study of high doses of the topoisomerase I inhibitor topotecan with granulocyte colony-stimulating factor in patients with solid tumours. J Clin Oncol 1996;14:1224–35.
41. Millward MJ, Webster LK, Toner GC, *et al.* Carboplatin dosing based on measurement of renal function-experience at the Peter MacCallum Cancer Institute. Aust NZ J Med 1996;26:372–9.
42. Calvert AH, Newell DR, Gumbrell LA, *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989;7:1748–56.
43. Chapple P, Prince HM, Quinn M, *et al.* Peripheral blood CD34-positive cell count reliably predicts autograft yield. Bone Marrow Transplantation 1998;22:125–30.
44. Cheng MF, Chatterjee S, Berger NA. Schedule-dependent cytotoxicity of topotecan alone and in combination chemotherapy regimens. Oncol Res 1994;6:269–79.
45. Chou TC, Motzer RJ, Tong Y, *et al.* Computerized quantitation of synergism and antagonism of taxol, topotecan, and cisplatin against human teratocarcinoma cell growth: a rational approach to clinical protocol design. J Natl Cancer Inst 1994;86:1517–24.
46. Faucette SR, McCune JS, Donahue AE, *et al.* Impact of carboplatin sequence on myelosuppression and systemic exposure of topotecan in small cell lung cancer. Proc Am Soc Clin Oncol 1999;18:210a–807.
47. Stiff PJ, Bayer R, Kerger C, *et al.* High-dose chemotherapy with autologous transplantation for persistant/relapsed ovarian cancer: a multivariate analysis of survival for 100 consecutively treated patients. J Clin Oncol 1997;15:1309–17.
48. Legros M, Dauplat J, Fleury J, *et al.* High-dose chemotherapy with hematopoietic rescue on patients with stage III to IV ovarian cancer: long-term results. J Clin Oncol 1997;15:1302–8.
49. Viens P, Maraninchi D, Legros M, *et al.* High dose melphalan and autologous marrow rescue in advanced epithelial ovarian carcinomas: a retrospective analysis of 35 patients treated in France. Bone Marrow Transplantation 1990;5:227–33.
50. Holmberg LA, Demirer T, Rowley S, *et al.* High-dose busulfan, melphalan and thiotepa followed by autologous peripheral blood stem cell resuce in patients with advanced stage III/IV ovarian cancer. Bone Marrow Transplantation 1998;22:651–9.
51. Stiff PJ, Shpall EJ, Tan S, *et al.* High dose combination chemotherapy and bone marrow rescue for ovarian carcinoma: current status in the United

States. Autologous marrow and blood transplantation. Dicke KA, Keating A, editors. Proceedings of the Seventh International Symposium, Arlington, Texas. Arlington, TX: The Cancer Treatment Research and Educational Institute, 1995:453–8.

52. Mulder NH, Aalders JG, Mulder POM, *et al.* High-dose chemotherapy with autologous bone marrow transplantation in ovarian cancer. Autologous marrow and blood transplantation, *In* Dicke KA, Keating A, editors. Proceedings of the Seventh International Symposium, Arlington, TX: The Cancer Treatment Research and Educational Institute, 1995:459–64.
53. Herben VMM, Nannan Panday VR, Richel DJ, *et al.* Phase I and pharmacologic study of the combination of paclitaxel, cisplatin, and topotecan administerd intravenously every 21 days as first-line therapy in patients with advanced ovarian cancer. J Clin Oncol 1999;17:747–55.
54. Kushner BH, Kramer K, Cheung NKV. Topotecan and high-dose cyclophosphamide: salvage therapy for pediatric solid tumors. Proc Am Soc Clin Oncol 1999;18:564a–2176.
55. Donato M, Gershenson D, Wharton JT, *et al.* Phase I study of high-dose topotecan and alkylating agents for advanced ovarian cancer. Proc Am Soc Clin Oncol 1999;18:44a–164.
56. Rella V, Noguera W, Smith D, *et al.* Phase I/II trial of multicycle paclitaxel/carboplatin/topotecan/etoposide/thiotepa with peripheral blood progenitor support in ovarian cancer. Proc Am Soc Clin Oncol 1999;18: 373a–1438.
57. Lind M, Ghazal-Aswad S, Gumbrell L, *et al.* Phase I study of pharmacologically based dosing of carboplatin with filgrastim support in women with epithelial ovarian cancer. J Clin Oncol 1996;14:800–5.
58. Schilder RJ, Johnson S, Gallo J, *et al.* Phase I trial of multiple cycles of high-dose chemotherapy supported by autologous peripheral blood stem cells. J Clin Oncol 1999;17:2198–207.
59. Schilder RJ, Gallo JM, Johnson SW, *et al.* Phase I study of multiple cycles of high dose topotecan, carboplatin and paclitaxel with peripheral blood stem cell support. Proc Am Soc Clin Oncol 1998;17:75a–290.
60. van Warmerdam LJ, ten Bokkel Huinink WW, Rodenhuis S, *et al.* Phase I clinical and pharmacokinetic study of topotecan administered by a 24-hour continuous infusion. J Clin Oncol 1995;13:1768–76.
61. Abbruzzese JL, Madden T, Schmidt S, *et al.* Phase I trial of topotecan administered by 24-hour infusion without and with G-CSF. Proc AACR 1993;34:329–1957.
62. Markman M, Blessing J, DeGeest K, *et al.* Lack of efficacy of 24-h infusional topotecan in platinum-refractory ovarian cancer: a Gynecologic Oncology Group trial. Gynecol Oncol 1999;75:444–6.
63. Hoskins P, Eisenhauer E, Beare S, *et al.* Randomized phase II study of two schedules of topotecan in previously treated patients with ovarian cancer: a National Cancer Institute of Canada Clinical Trials Group study. J Clin Oncol 1998;16:2233–7.