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

John D. Hainsworth, M.D.
Howard A. Burris III, M.D.
Lisa H. Morrissey, B.B.S.
F. Anthony Greco, M.D.

Sarah Cannon-Minnie Pearl Cancer Center, Centennial Medical Center, Nashville, Tennessee.

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Address for reprints: John D. Hainsworth, M.D., Sarah Cannon Cancer Center, Centennial Medical Center, 250 25th Avenue, No., Suite 412, Nashville, TN 37203.

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BACKGROUND. Topotecan is a new antineoplastic agent with a broad spectrum of activity. The purpose of this Phase I trial was to define the maximum tolerated dose of topotecan when added to the widely used combination of paclitaxel and carboplatin.

METHODS. Patients with advanced cancer that was refractory or resistant to standard treatments were treated with paclitaxel, carboplatin, and topotecan; doses were escalated in sequential cohorts of patients. After definition of the maximum tolerated dose without cytokines, granulocyte-colony stimulating factor (G-CSF) was added and further dose escalation was attempted.

RESULTS. The maximum tolerated doses were: paclitaxel, 135 mg/m^2, as a 1-hour intravenous (i.v.) infusion on Day 1; carboplatin, area under the curve 5.0, on Day 1; and topotecan, 0.75 mg/m^2, i.v. on Days 1, 2, and 3; the regimen was repeated every 21 days. Myelosuppression, particularly thrombocytopenia, was the dose-limiting toxicity with this three-drug combination. Nonhematologic toxicity was uncommon. The addition of G-CSF did not allow substantial dose escalation because thrombocytopenia was uneffected by this agent. Eleven of 25 patients had major responses to this combination, including 8 of 14 patients with previously treated small cell lung carcinoma.

CONCLUSIONS. The combination of paclitaxel, carboplatin, and topotecan is feasible, although only relatively low doses of all three drugs can be tolerated due to myelosuppression. This regimen showed a high level of activity in these patients with refractory cancer, and merits further investigation. ***Cancer*** **1999;85:1179–85.**
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The combination of paclitaxel and carboplatin is one of the most active and widely used treatment regimens in clinical oncology. This combination currently is a standard treatment regimen for ovarian carcinoma and nonsmall cell lung carcinoma and also is highly active in breast carcinoma, head and neck carcinoma, esophageal carcinoma, and bladder carcinoma.[1–7] In addition to its high level of efficacy, the paclitaxel/carboplatin combination is relatively well tolerated, with cumulative peripheral neuropathy as the dose-limiting toxicity (DLT). The myelosuppression from this regimen is moderate in the majority of patients, and has been found to be less severe than originally was anticipated. A protective effect of paclitaxel on the bone marrow, particularly megakaryocytes, has been postulated, although the mechanism still is unclear.

Topotecan, a topoisomerase I inhibitor, recently demonstrated activity against a variety of tumors. In a randomized trial, the activity of topotecan was comparable to that of paclitaxel in patients with recurrent ovarian carcinoma.[8] Substantial second-line activity in patients with small cell lung carcinoma also has been demonstrated recently.[9] When administered by a standard divided dose intravenous (i.v.) schedule over 5 days, myelosuppression is the major toxicity of topotecan, and has made the development of combination regimens somewhat difficult. However, the demonstrated activity and distinct mechanism of action of topotecan provide compelling reasons to develop well tolerated combination regimens. The successful addition of topotecan to the paclitaxel/carboplatin combination may provide an improved first-line treatment regimen for ovarian carcinoma, small cell lung carcinoma, and other malignancies.

In this Phase I trial, we report the results of a dose-finding study in which paclitaxel, carboplatin, and a 3-day i.v. schedule of topotecan were administered to patients with advanced, refractory cancer. Maximum tolerated doses (MTD) were determined with and without the use of granulocyte-colony stimulating factor (G-CSF), and the results reported here.

PATIENTS AND METHODS

Beginning in January 1997, patients with biopsy-proven, advanced, incurable malignancies were entered into this Phase I trial. Patients were required to have tumors refractory to standard treatments or to have tumor types for which standard treatments were considered ineffective. Eligible patients could have received no more than two previous chemotherapy regimens. Additional entry criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; measurable or evaluable disease; normal bone marrow, liver, and kidney function; no previous treatment with topotecan; and age < 18 years. All patients were required to be at least 4 weeks from any previous chemotherapy, and at least 2 weeks from previous radiation therapy. This study was approved by the Institutional Review Board at Centennial Medical Center, and signed written informed consent was obtained from all patients prior to study entry.

This study was performed using a standard Phase I design, with sequential cohorts of three to five patients receiving escalating doses of chemotherapeutic agents until an MTD of each drug was identified. The number of patients targeted for each dose level was made flexible because some patients with advanced, refractory cancer experience rapid disease progression or have other unexpected complications, and become inevaluable. If patients accrued rapidly at a given dose level, then five patients (rather than the traditional three patients) were entered. However, if accrual was slower, then decisions regarding dose escalation could be made on the basis of three (or four) evaluable patients.

At the first dose level evaluated, paclitaxel, 135 mg/m^2 (1-hour i.v. infusion), and carboplatin, area under the curve (AUC) 5.0, were administered on Day 1, and topotecan, 1.0 mg/m^2, was administered by 30-minute i.v. infusion on Days 1, 2, and 3. Chemotherapy cycles were repeated at 21-day intervals for a maximum of 6 courses in responding patients. Paclitaxel was administered first, followed by carboplatin and then topotecan. Premedications for paclitaxel included: dexamethasone, 20 mg orally, 12 hours and 4 hours prior to administration, and dexamethasone, 20 mg i.v.; diphenhydramine, 50 mg i.v.; and cimetidine, 300 mg i.v., 30 minutes prior to paclitaxel administration. Carboplatin was administered using AUC dosing as described by Calvert et al: carboplatin dose = (glomerular filtration rate [GFR] + 25) $\times$ desired AUC.[10] GFR was calculated according to the Cockcroft-Gault formula:

$$\text{GFR} = \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum creatinine}} \times \begin{cases} 0.85 \text{ (female)} \\ 1.0 \text{ (male)} \end{cases}.$$

The doses of paclitaxel and carboplatin in the first dose level were chosen because these were believed to be the minimum effective doses based on previous experience with the paclitaxel/carboplatin regimen.

In the original study design, initial escalation of the topotecan dose was planned, followed (if possible) by escalation of the paclitaxel dose. However, dose-limiting myelosuppression was observed unexpectedly at the first dose evaluated, and doses were reduced to identify an MTD. The dose levels evaluated in this trial are included in Table 1.

In this trial, it was anticipated that myelosuppression would be the DLT. Dose-limiting myelosuppression included the following: 1) leukocyte nadir $<$ 500/μL for $>$4 days or resulting in hospitalization for the treatment of neutropenia and fever, 2) platelet nadir $<$ 50,000/μL for $>$4 days or bleeding episode associated with thrombocytopenia or requiring a platelet transfusion, or 3) leukopenia or thrombocytopenia on Day 21 requiring a treatment delay or dose reduction. Any other Grade 3 or 4 nonhematologic toxicity with the exception of alopecia, nausea, and emesis also was considered a DLT.

To determine the MTD, the number of episodes of DLT was determined for patients at each successive dose level during the first two courses of treatment. If a hematologic DLT was observed in two of the first

TABLE 1
Doses Evaluated

Dose level	No. of patients	Topotecan (mg/m^2, Days 1–3)	Paclitaxel (mg/m^2, Day 1)	Carboplatin (AUC, Day 1)	G-CSF
1	5	1.0	135	5.0	−
2	7	0.75	135	5.0	−
3	7	0.75	135	5.0	+
4	6	0.75	175	5.0	+

AUC: area under the curve; G-CSF: granulocyte-colony stimulating factor.

three patients entered at a dose level, or a nonhematologic DLT was observed in one of three, then three additional patients were added to the patients already evaluated at that dose level. If three of six patients at a dose level had hematologic DLT, or two of six had nonhematologic DLT, further dose escalation was stopped and the MTD defined as one level below that at which the DLT occurred.

Prior to beginning treatment, the following laboratory parameters were measured in all patients: complete blood counts, differential, chemistry profile, and electrolytes. In addition, all patients had an electrocardiogram and chest radiograph. Computerized tomography (CT) of the chest and abdomen was performed, and additional radiologic evaluation was performed as necessary to document the stage of cancer and provide tumor measurements. During therapy, complete blood counts were measured weekly. Electrolytes and chemistry profile were obtained every 3 weeks. During therapy, dose reductions were made on the basis of blood counts on the day of scheduled treatment. Full doses were administered if patients had a leukocyte count $\geq$3000/μL and a platelet count $\geq$100,000/μL. If patients had a leukocyte count 2000–3000/μL or a platelet count 75,000–100,000/μL, 75% doses of all agents were administered. If a leukocyte count was $<$2000/μL or a platelet count was $<$75,000/μL, treatment was delayed for 1 week and then resumed at 75% doses after the leukocyte count reached $>$2000/μL and the platelet count reached $>$75,000/μL. Patients who: 1) were admitted for the treatment of neutropenia and fever, 2) received a platelet transfusion, or 3) developed bleeding associated with thrombocytopenia had dose reductions of all drugs to 75% during subsequent treatment cycles.

After 2 courses of treatment (6 weeks), patients were reassessed for tumor response. Patients with stable disease or evidence of objective response continued treatment until disease progression or for a maximum of six courses. Response categories were assigned using standard definitions. Complete response required the total disappearance of clinically and radiologically detectable disease for at least 4 weeks. Partial response required at least a 50% reduction in the size of all measurable lesions as measured by the product of the greatest length and maximum width, with no new lesions appearing. Evaluable lesions were required to show objective improvement with accompanying symptomatic improvement. Patients with stable disease had a reduction by $<$50% or an increase by $<$25% in the size of lesions, with no new lesions appearing. All other patients were categorized as having progressive disease. All responses were confirmed at the time of a second restaging evaluation 6 weeks after the initial response assessment.

Between January 1997 and January 1998, 25 patients entered this clinical trial. Patient characteristics are summarized in Table 2. A relatively large proportion of patients in this trial had small cell lung carcinoma; we purposefully entered patients with recurrent small cell lung carcinoma on this trial due to the known activity of these agents. The four patients who had not received previous chemotherapy had inherently refractory tumor types (melanoma [one patient] gastric carcinoma [one patient], cholangiocarcinoma [one patient], and mesothelioma [one patient].

RESULTS

After five patients were entered at the initial dose level, it became clear that dose-limiting myelosuppression had been reached even at this first dose level. All 5 patients had platelet nadirs $<$50,000/μL (median nadir, 26,000/μL), and 3 patients required platelet transfusions. Grade 4 neutropenia occurred in four patients but only one patient required hospitalization for neutropenia and fever.

Because of this DLT at the first dose level, a second cohort of patients was treated at a lower dose level to define the MTD (Table 1). Because the doses of all three agents were lower than expected, we then chose to add G-CSF and attempt reescalation of the doses to determine the MTD with G-CSF. The four dose levels evaluated are shown in Table 1.

TABLE 2
Patient Characteristics (N = 25)

Characteristic	No. of patients (%)
Median age (yrs) (range)	62 (26–77)
Gender (male/female)	14/11
ECOG performance status	
0	5
1	20
Tumor type	
Lung carcinoma, small cell	14
Lung carcinoma, nonsmall cell	3
Melanoma	2
Adenocarcinoma, unknown primary	2
Ovarian	1
Gastric	1
Cholangiocarcinoma	1
Esophageal	1
No. of previous regimens	
0	4
1	20
2	1
Previous paclitaxel	7
Previous platinum	3

ECOG: Eastern Cooperative Oncology Group.

TABLE 3
Treatment-Related Toxicity

	No. of patients			
Dose level	**1**	**2**	**3**	**4**
No. of patients treated	5	7	7	6
Myelosuppression				
Leukopenia				
Grade 3	4	2	1	1
Grade 4	1	0	0	1
Thrombocytopenia				
Grade 3	2	3	3	5
Grade 4	3	1	3	3
Hospitalization, neutropenia/fever	1	0	0	0
Platelet transfusions	2	1	2	0
Bleeding episodes	0	0	0	1
RBC transfusions	1	2	2	2
Nonhematologic toxicity (Grade 3/4)				
Nausea/emesis	0	0	0	0
Diarrhea	0	0	0	0
Peripheral neuropathy	1	0	0	0
Arthralgia/myalgia	0	0	1	0
Rash	0	0	0	1

RBC: red blood cell.

Treatment-Related Toxicity

Table 3 outlines the incidence of treatment-related toxicity for the four dose levels evaluated in this trial. Myelosuppression and complications of myelosuppression were the only common Grade 3/4 toxicities observed. Grade 3 or 4 thrombocytopenia was observed at each dose level and was more severe than leukopenia. In general, the duration of thrombocytopenia was brief, and patients experiencing Grade 3 thrombocytopenia developed no complications and did not require platelet transfusions. Conversely, five of ten patients experiencing Grade 4 thrombocytopenia required platelet transfusions and one of these patients had an episode of gastrointestinal bleeding.

Leukopenia was a problem at the first dose level (paclitaxel, 135 mg/m^2, on Day 1; carboplatin, AUC 5.0, on Day 1; and topotecan, 1.0 mg/m^2, on Days 1–3), with all 5 patients experiencing either Grade 3 or 4 leukopenia and 1 patient requiring hospitalization for neutropenia and fever. Like thrombocytopenia, leukopenia generally was of brief duration, and after reducing the topotecan dose from 1.0 to 0.75 mg/m^2 (dose level 2), leukopenia occurred in only 2 of 7 patients. The addition of G-CSF appeared to be effective in minimizing leukopenia; even with the escalation of paclitaxel from 135 to 175 mg/m^2, only 2 of 6 patients developed Grade 3/4 leukopenia, and none of these patients had febrile neutropenia. Cumulative anemia with repeat courses was observed at each dose level, and a total of 7 patients (28%) required transfusions at some time during treatment.

Grade 3/4 nonhematologic toxicity was uncommon, and bore no relation to dose level. Grade 3 peripheral neuropathy, arthralgia/myalgia, and rash each were observed in one patient.

Maximum Tolerated Dose

In the absence of cytokines, the second dose level evaluated (paclitaxel, 135 mg/m^2, on Day 1; carboplatin, AUC 5.0, on Day 1; and topotecan, 0.75 mg/m^2 on Days 1–3) was the MTD. Because the major DLT with this regimen was thrombocytopenia, the addition of G-CSF did not allow a substantial increase in dose. When the paclitaxel dose was increased from 135 mg/m^2 to 175 mg/m^2 (dose level four), the severity of leukopenia did not increase but Grade 4 thrombocytopenia was observed in 3 of 6 patients treated. Therefore, the MTD was not changed by the addition of G-CSF.

Treatment Efficacy

In spite of the relatively low doses of the agents tolerated in this 3-drug regimen, 11 of 25 patients had a major response (Table 4). In particular, responses were observed in 8 of 14 patients with previously treated small cell lung carcinoma. All these patients had previously received treatment with either carboplatin and etoposide (six patients) or paclitaxel, car-

TABLE 4
Treatment Efficacy

Tumor type	No. of patients	Overall PR/CR (%)	CR
Small cell lung carcinoma	14	8 (57%)	1
Nonsmall cell lung carcinoma	2	0	0
Melanoma	2	1 (50%)	1
Adenocarcinoma, unknown primary	2	0	0
Gastric carcinoma	1	1 (100%)	0
Ovarian carcinoma	1	1 (100%)	0
Cholangiocarcinoma	1	0	0
Esophageal carcinoma	1	0	0
Mesothelioma	1	0	0

PR: partial response; CR: complete response.

boplatin, and etoposide (two patients). All 8 responders previously had responded to first-line treatment, and 5 of these 8 had been off treatment for >3 months prior to receiving this regimen. Additional responses were observed in patients with malignant melanoma, gastric carcinoma, and ovarian carcinoma. The patient with melanoma had received no previous chemotherapy, and had multiple subcutaneous scalp nodules and cervical adenopathy. He achieved a complete response after 2 courses of this regimen, and remained in continuous complete response 10 months after treatment. The patient with advanced ovarian carcinoma had developed progressive liver metastases within 3 months of completing a course of paclitaxel and carboplatin. After six courses of this regimen, she had a normal CA 125 level and a near-complete response on CT scan.

DISCUSSION

Since its introduction into clinical practice, the clinical development of topotecan has been delayed somewhat by the marked myelosuppression observed with the 5-day i.v. administration schedule. In patients with advanced ovarian carcinoma, topotecan proved as effective as paclitaxel in platinum-refractory patients, although myelosuppression was considerably more severe.[8] Marked activity also has been demonstrated in previously treated patients with small cell lung carcinoma, in which the activity of single agent topotecan was equivalent to the combination of cyclophosphamide, doxorubicin, and vincristine in patients who had responded to previous chemotherapy and had been off treatment for ≥60 days.[11] Clinical activity also has been demonstrated in a variety of other tumor types including hematologic malignancies, brain tumors, and nonsmall cell lung carcinoma.[12–14] Despite this well documented activity, the predominant current use of topotecan remains as a single agent in previously treated patients. Attempts to combine this agent with cisplatin produced unacceptable toxicity, predominantly myelosuppression.[15,16] Early attempts to combine topotecan with etoposide as a topoisomerase I/topoisomerase II blockade also met with unexpectedly severe myelosuppression.[17]

The paclitaxel/carboplatin combination has emerged as a well tolerated outpatient regimen that is highly active in a variety of advanced malignancies.[1–7] Although myelosuppression is moderate with this regimen, it is nearly exclusively limited to leukopenia, and has been minimized by the administration of paclitaxel by short infusion. Overall toxicity with the paclitaxel/carboplatin combination has been limited enough to allow several drugs to be evaluated as "third agents" when added to this regimen. Etoposide, gemcitabine, and vinorelbine each have been added to the paclitaxel/carboplatin combination with acceptable toxicity, and the efficacy of these regimens currently is being evaluated.[18–21]

In this Phase I study we evaluated the three-drug combination of paclitaxel, carboplatin, and topotecan. Because we anticipated that myelosuppression would be a major factor with this regimen, we began with what we considered to be minimally effective doses of paclitaxel and carboplatin (135 mg/m^2 and AUC 5.0, respectively). We also shortened the 5-day administration schedule of topotecan to 3 days, again in an attempt to minimize myelosuppression. Patients entering the trial were required to have a good ECOG performance status (0 or 1) and a maximum of two previous chemotherapy regimens.

In spite of the low doses of all three agents used in the starting dose level, a further modest dose reduction was necessary before we could identify the MTD. In reducing doses from the initial levels, we decided to retain the initial doses of paclitaxel and carboplatin and decrease the topotecan dose from 1.0 to 0.75 mg/m^2 given on 3 consecutive days. Myelosuppression, particularly thrombocytopenia, was the DLT of this regimen. As expected, the duration of leukopenia and thrombocytopenia was brief, and the majority of patients developing Grade 3 thrombocytopenia required no intervention and developed no complications. Aside from myelosuppression and its complications, this regimen was well tolerated.

Because the major DLT of this regimen was thrombocytopenia, it is not surprising that the addition of G-CSF did not allow substantial dose escalation of any of the drugs. At the MTD, the addition of G-CSF may have minimized leukopenia, but it did not alter the side effect of profile of the regimen substantially. When paclitaxel was escalated from 135 mg/m^2 to 175

mg/m^2 (with G-CSF), leukopenia generally was not a problem, but Grade 4 thrombocytopenia remained frequent. Therefore, we do not recommend the routine use of G-CSF with this regimen; however, its use may be necessary in patients receiving repeated courses to minimize leukopenia.

As one of the few "standard dose" chemotherapy regimens that produces more thrombocytopenia than leukopenia, this regimen provides an ideal setting in which to test the new thrombopoietin agents. We currently are evaluating dose escalations of topotecan in conjunction with thrombopoietin, because substantial dose escalations may be possible if thrombocytopenia is ameliorated.

In spite of the relatively low doses of all three agents, this regimen proved highly active in this population of patients with refractory cancer. The observation of 8 major responses (with 1 complete response) in 14 patients with previously treated small cell lung carcinoma is of considerable interest because the majority of regimens in this setting produce response rates of $<40\%$. The first-line combination of paclitaxel and topotecan has shown a high level of activity in a small number of patients with extensive disease, producing a 92% response rate and a median survival of >12 months.[22] We currently are evaluating this combination of paclitaxel, carboplatin, and topotecan in the first-line treatment of patients with small cell lung carcinoma. This three-drug regimen also has possibilities for the first-line treatment of ovarian carcinoma. However, the incremental value of adding topotecan to the highly active paclitaxel/carboplatin combination currently is unknown, and will require further clinical evaluation.

The introduction of several active new antineoplastic agents during the last several years has created numerous possibilities to improve treatment for patients with advanced cancer. The development of new, effective, well tolerated combination regimens is one important strategy to allow the new drugs to be evaluated in a front-line treatment setting. Although the use of topotecan at "standard" doses and schedules has made the development of well tolerated combinations relatively difficult, it is possible that substantially lower doses may retain excellent activity. In this sense, topotecan may resemble etoposide because both drugs exhibit marked schedule dependency. If these speculations prove true, further development of topotecan will be facilitated greatly, and may improve the treatment of several common malignancies.

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