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Phase I and pharmacologic study of sequential topotecan-carboplatin-etoposide in patients with extensive stage small cell lung cancer

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Summary The inhibition of topoisomerase I by topotecan results in a compensatory increase in topoisomerase II associated with increased in vitro sensitivity of tumors to etoposide. Maximal synergy has been observed for the sequence of topotecan followed by etoposide. Carboplatin has clinical activity when combined with either of these two agents. These interactions were the pharmacologic rationale for topotecan p.o. days 1–5, carboplatin i.v. day 6, and etoposide p.o. days 6–10. Three successive dose levels were explored: (1) topotecan 2 mg/day, carboplatin AUC 5, etoposide 150 mg/day; (2) topotecan 3 mg/day, carboplatin AUC 5, etoposide 150 mg/day; and (3) topotecan 3 mg/day, carboplatin AUC 5, etoposide 200 mg/day. Filgrastim 5 µg/kg/day was injected s.c. days 11–18. Up to 6 cycles were administered every 21 days. Eligible patients had measurable or evaluable, extensive disease, small lung cell lung cancer, no prior chemotherapy, ECOG performance status 0–2, and adequate hematologic, renal, and hepatic function. Follow-up was weekly for CBC. Tumor response was assessed after 2 and 6 cycles. Dose limiting toxicity (DLT) was defined as any of the following in cycle 1: grade 3 or 4 non-hematologic toxicity other than nausea and vomiting, grade 4 neutropenia lasting more than 3 days, neutropenic fever or sepsis, grade 4 thrombocytopenia, or failure to recover neutrophils $\geq 1500/\mu\text{l}$ or platelets $\geq 100,000/\mu\text{l}$ by day 28. Ten patients were enrolled: median age 62 (range, 50–79); female/male 4/6; and performance status 0/1/2 in 2/7/1. Three patients each were treated on dose levels 1 and 2 without DLT. The first 2 patients entered on dose level 3 had no DLT. The third patient on dose level 3 developed grade 4 neutropenia lasting more than 3 days, neutropenic fever, and grade 4 thrombocytopenia on day 15 of cycle 1. The fourth patient on dose level 3 developed grade 4 thrombocytopenia on day 18 of cycle 1. One patient received only 1 cycle and was not evaluable for response. Seven patients completed 6 cycles: 1

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had a complete response and 6 achieved a partial response. The third patient on dose level 3 received 2 cycles and had stable disease, but had to be removed from protocol treatment because of grade 4 neutropenia despite dose reduction in cycle 2. The fourth patient on dose level 3 achieved a partial response, but had to be removed from protocol therapy after cycle 5 because of recurrent grade 4 thrombocytopenia. In conclusion, neutropenia and thrombocytopenia were dose-limiting. The maximum tolerated dose (MTD) is topotecan 3 mg/day p.o. days 1–5, carboplatin AUC 5 i.v. day 6, and etoposide 150 mg/day p.o. days 6–10 with filgrastim.

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1. Introduction

When investigators from the National Cancer Institute (NCI) reviewed 20 years of phase III trials for patients with extensive stage small cell lung cancer (SCLC), they found 21 cooperative group phase III studies in the NCI Cancer Therapy Evaluation Program database from 1972 to 1993 [1]. The median of the median survival times of patients treated on the control arms of the trials initiated between 1972 and 1981 was 7.0 months; for those patients enrolled onto control arms between 1982 and 1990, the median survival time was 8.9 months ($p=0.001$). They concluded that this 2 month prolongation in median survival over this time period was a modest improvement. Looking at the trials in more detail, they found that 5 of the 21 randomized phase III trials showed a significant improvement of the investigational arm over the control arm at the $p<0.05$ level. Here again, the gain in median survival was 2 months. Interestingly, these were the 5 trials that added new agents to the combination chemotherapy. The remaining 16 trials showed no improvement of the investigational over the control arm; these were studies that tried different regimens of cyclophosphamide or etoposide/cisplatin. Therefore, it appears reasonable to attempt to integrate new active agents in the front-line therapy of this disease. A recent NCI Intergroup phase III trial compared etoposide and cisplatin with etoposide, cisplatin, and paclitaxel and demonstrated that the addition of paclitaxel to etoposide and cisplatin resulted in increased toxicity but no survival advantage [2]. We sought to investigate a three-drug combination with a pharmacologic rationale.

The combination of topoisomerase I and II inhibitors appeared to be synergistic when given sequentially and antagonistic when given simultaneously [3]. Cellular topoisomerase II levels increased 24–48 h after in vitro exposure to a topoisomerase I inhibitor, which accounts for the synergistic effect of topotecan followed by etoposide [4]. Whitacre et al. studied athymic mice bearing SW 480 human colon cancer xenografts to elucidate the effect of topoisomerase I inhibitors on the modulation of topoisomerase II levels and sensitivity of topoisomerase II-directed drugs and treated them with simultaneous, subsequent, or distant doses of topotecan and etoposide [5]. The simultaneous administration of topotecan and etoposide resulted in an antagonistic response. In contrast, inhibition of topoisomerase I by topotecan resulted in a compensatory increase in topoisomerase II levels associated with increased sensitivity of tumors to subsequent treatment with etoposide. Bonner and Kozelsky demonstrated in V79 cells (hamster lung fibroblasts) that the maximum synergy occurs for the sequence of topotecan followed by etoposide (as compared

to the opposite sequence) [6]. Similar sequence-specific effects were noted for irinotecan and etoposide [7]. Thus, there is a pharmacologic rationale for the sequence of a topoisomerase I inhibitor followed by a topoisomerase II inhibitor.

Topoisomerase I inhibitors, in particular topotecan, exhibited synergistic effects with cisplatin in vitro [8,9]. The sequence of cisplatin [10,11] or carboplatin [12,13] followed by topotecan has more hematologic toxicity than topotecan followed by the platinum drug. Therefore, the sequence topotecan followed by carboplatin was chosen for this trial. Clinical synergism has also been observed for the combination of cisplatin and etoposide in SCLC when etoposide followed the administration of cisplatin [14]. The combination of cisplatin and etoposide has been used extensively for the treatment of SCLC [15]. A review of the comparative pharmacology and clinical activity of cisplatin and carboplatin supports the view that carboplatin can be substituted for cisplatin in the treatment of extensive-stage SCLC [16–18]. These considerations resulted in the sequence of topotecan-carboplatin-etoposide.

Both topotecan and etoposide are available as oral formulations which makes prolonged administration and thereby inhibition of their target enzymes (topoisomerase I and II) feasible. Von Pawel et al. found oral topotecan to be similar in efficacy to intravenous topotecan in the treatment of patients with relapsed SCLC with less grade 4 neutropenia and greater convenience of administration [19]. Gerrits et al. compared the clinical pharmacodynamics of different administration schedules of oral topotecan [20]. The schedule rather than the area under the concentration versus time curve (AUC) seemed to be related to the type of toxicity: Prolonged 21-day oral administration resulted in intestinal side effects (mainly diarrhea) as a dose-limiting toxicity. The 5-day administration resulted in neutropenia. The oral formulation of topotecan has a bioavailability of 32–44%. The maximum tolerated dose for oral topotecan as a single agent is 2.3 mg/m²/day administered as a gelatin capsule for 5 days every 21 days. Etoposide also has known schedule-dependent effects and is generally given over 3–5 days [21–23].

Oral etoposide has similar activity as intravenous etoposide [24] and is available in the United States only in 50 mg capsules. Topotecan is available in 1.0 mg and 0.25 mg capsules. Rounding of the calculated dose to the nearest capsule size is necessary in studies of oral etoposide or oral topotecan that use dosing in mg/m² based on body-surface area (BSA). Thus, depending on the patient's BSA, 'accurate' dosing is often not possible. In addition, in the case of topotecan, patients may be required to take different

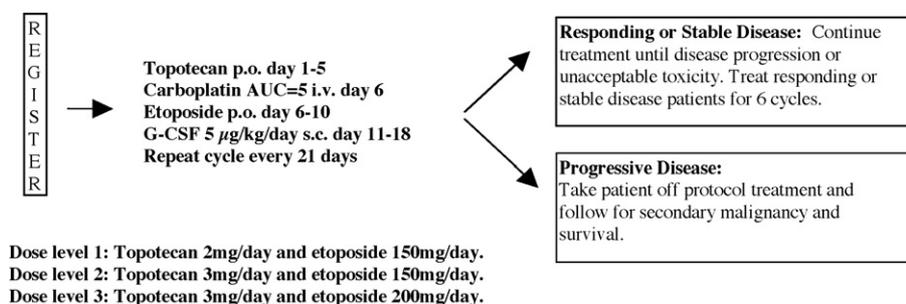


Fig. 1 Study schema.

capsule sizes, which may lead to poor adherence to the planned dosing regimen. This may in turn affect safety (e.g., a patient mistakes a 1.0 mg capsule for a 0.25 mg capsule) and clinical response. However, the concept of BSA-based dosing has been called into question [25–32]. A scientific basis for dosing anticancer drugs, including etoposide and topotecan, in humans based on BSA is lacking [25–32,33,34]. Loos et al. studied the inter- and intra-patient variability of the pharmacokinetics of oral topotecan and convincingly argued that there is no advantage of BSA-based dosing over a fixed dose regimen [34]. This was the rationale for the use of fixed doses of topotecan and etoposide in the current study.

The main objective was to determine the toxicity profile and the maximum tolerated dose (MTD) of the chemotherapy regimen of sequential topotecan, carboplatin, and etoposide in chemotherapy naïve patients with extensive-stage small-cell lung cancer. We also studied the pharmacology of topotecan and etoposide.

2. Materials and methods

2.1. Patient eligibility

All patients were required to have histologically or cytologically documented SCLC and extensive stage disease. Patients had measurable or evaluable disease. The study protocol was reviewed and approved by the Institutional Review Board of Wake Forest University School of Medicine. Each patient had to be aware of the nature of his/her disease and had to willingly give written informed consent after being informed of the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. The eligibility criteria included: age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; and life expectancy > 2 months. Females had to be non-pregnant and non-nursing because of significant risks to the fetus or infant. No prior chemotherapy was allowed. Prior radiation was only allowed for brain metastasis, but patients had to be neurologically stable. The required laboratory values at entry included: absolute neutrophil count (ANC) $\geq 1500/\mu\text{l}$; platelet count $\geq 100,000/\mu\text{l}$; serum creatinine ≤ 1.5 mg/dl; and total bilirubin ≤ 1.5 mg/dl. Patients had to be able to swallow capsules because treatment depended on their compliance with oral topotecan and etoposide. Other serious medical or psychiatric illness precluded participation in this trial.

2.2. Treatment

The treatment schema and dose levels are shown in Fig. 1. The carboplatin dose was fixed at an AUC of 5 which was calculated using the Calvert formula [35] as follows: carboplatin dose = $5 \times (\text{creatinine clearance} + 25)$. The creatinine clearance was estimated for each treatment cycle using the Cockcroft-Gault formula [36]. The commercially available formulation of carboplatin was infused i.v., over 30 min. The fixed (rather than BSA-based) doses for oral topotecan and etoposide were escalated as shown in Fig. 1. This dose escalation proceeded in cohorts of three patients if no dose-limiting toxicity (DLT) was observed. Oral topotecan was provided by SmithKline Beecham Pharmaceuticals (Collegeville, PA) in 1.0 mg capsules. The marketed formulation of etoposide was prescribed. Toxicity was graded according to the NCI Common Toxicity Criteria, version 2.0 (<http://ctep.info.nih.gov>). Complete blood counts were obtained weekly. DLT was defined as: grade 3 or 4 non-hematologic toxicity other than nausea and vomiting; grade 4 neutropenia lasting more than 3 days; neutropenic fever or sepsis; grade 4 thrombocytopenia; and failure to recover neutrophils $\geq 1500/\mu\text{l}$ or platelets $\geq 100,000/\mu\text{l}$ by day 28 from start of treatment. DLT occurring in the first treatment course was used to make the following decisions: If 0 out of 3 patients at a given dose level had DLT, escalation proceeded to the next dose level. If 1 out of 3 patients had DLT, up to 3 additional patients were entered at that dose level. If none of the second cohort of 3 patients experienced DLT, then the dose was to be escalated. If 2 or more patients at a given dose level had DLT, dose escalation ceased and the next lower level was called the MTD. Because neutropenia was anticipated to be dose-limiting, filgrastim (granulocyte-colony stimulating factor, G-CSF) was used.

Patients who initially presented with brain metastases received whole-brain irradiation prior to the chemotherapy. Patients who subsequently developed brain metastases were considered to have progressive disease and taken off protocol. Patients without brain metastases at initial presentation who achieved a complete remission were to receive prophylactic whole-brain irradiation. No other radiation therapy was administered while patients were on this protocol.

Complete blood counts were obtained weekly. Patients were evaluated before every treatment cycle, and treatment was initiated only if the granulocyte count was $\geq 1500/\mu\text{l}$ and the platelet count was $\geq 100,000/\mu\text{l}$. Tumor response was assessed after 2 and 6 cycles of therapy according to the Response Evaluation Criteria in Solid Tumors

(RECIST) by the NCI (<http://ctep.info.nih.gov>). Responding patients remained on protocol for up to 6 cycles of the three-drug combination. Thereafter, all patients were observed and allowed to receive second line chemotherapy or radiation for relapse or progressive disease.

2.3. Pharmacokinetics

A sparse sampling design was used, in which samples were collected during designated sampling windows. Sparse sampling designs are advantageous because they do not require strict adherence to a rigorous schedule and they reduce the amount of time that study participants are required to spend in the clinic. Hashimoto and Sheiner showed using simulations that, compared with fixed sampling times, designs in which sampling times are varied among participants are more robust in protecting against mis-specifying the pharmacokinetic model [37]. In addition, both the ability to identify the model and the ability to predict individual parameter values are improved when more than one sample is taken per patient [38]. Samples were taken on day 1 for topotecan measurements: baseline before the first oral dose of topotecan; between 30 and 90 min, 120 and 180 min, and 210 and 300 min after first dose of topotecan. On day 6, a sample was taken just before the first dose of etoposide for topotecan measurement and as a baseline for etoposide. Then samples were taken for etoposide measurements: between 30 and 90 min, 120 and 180 min, and 210 and 300 min after first dose of etoposide; and on day 11 between 20 and 28 h after the last etoposide dose. Pharmacokinetic samples were obtained in the first three cycles of therapy. Plasma concentrations of topotecan as the total of the lactone and carboxylate were measured by high performance liquid chromatography (HPLC) as in previously published work [39]. Plasma samples were also analyzed for etoposide concentrations by HPLC as in previously published work [40].

Adapt II software was used for pharmacokinetic data analysis (Biomedical Simulation Resource, Los Angeles, CA) [41]. A one-compartment model with first order absorption and an absorption lag time was fit to each patient's topotecan data. A two-compartment model with first order absorption was fit to each patient's etoposide data. Each model was fit to the concentration-time data using a Bayesian algorithm as implemented in ADAPT II software. Prior parameter

distributions were derived from the literature [42,43]. The final population estimates were then used to refine the initial population values. All data sets were again fit and the values obtained were considered the final estimate.

3. Results

3.1. Phase I

Ten patients were enrolled. Their median age was 62 years (range, 50–79). Four were females and 6 were males, and all were Caucasians. Table 1 summarizes the results. Three patients each were treated on dose levels 1 and 2 without DLT. Patient #1 completed one cycle and developed a stroke unrelated to protocol therapy. She therefore discontinued participation in the study. The first 2 patients entered on dose level 3 had no DLT. Patient #9 on dose level 3 developed grade 4 neutropenia lasting more than 3 days, neutropenic fever, and grade 4 thrombocytopenia on day 15 of cycle 1. This was the first event of DLT. Per protocol, patient #9 received the second cycle with topotecan and etoposide per dose level 2 and carboplatin at an AUC of 4. Patient #9 again developed grade 4 neutropenia lasting more than 3 days and was removed from the study. Patient #10 on dose level 3 developed grade 4 thrombocytopenia on day 18 of cycle 1. This was the second event of DLT and accrual ceased per protocol. Dose level 2 was deemed the MTD. Patient #10 was removed from the study after cycle 5 because of recurrent grade 4 thrombocytopenia despite dose reductions.

The predominant toxicity was myelosuppression which is shown in Table 2 for cycle 1 and for all cycles. In addition to patient #9, 3 other patients had neutropenia that was not dose-limiting in cycle 1. Besides patients #9 and 10, one other patient had thrombocytopenia that was not dose-limiting in cycle 1. Reversible neutropenia, thrombocytopenia, and anemia were the dominant toxicities in cycle 1 and overall. Two patients had grade 3 neutropenic infections. No non-hematological toxicities of grade 3 and 4 severity were observed. No patient died as a result of protocol therapy.

Patient #1, who received only one treatment cycle, was not evaluable for tumor response. Seven patients completed 6 cycles. One had a complete response and 6 achieved a partial response (Table 1). The 2 patients with DLT received less than 6 cycles: patient #9 showed stable disease after 2 cycles

Table 1 Study summary

Patient number	Dose level	Performance status	Number of cycles	DLT	Response
1	1	1	1	No	NE
2	1	1	6	No	PR
3	1	0	6	No	PR
4	2	1	6	No	PR
5	2	0	6	No	PR
6	2	1	6	No	PR
7	3	1	6	No	PR
8	3	2	6	No	CR
9	3	1	2	Yes	SD
10	3	1	5	Yes	PR

Abbreviations: DLT, dose limiting toxicity (see text); NE, not evaluable; PR, partial response; CR, complete response; SD, stable disease.

Table 2 Grade of toxicity in cycle 1 and over all cycles

Patient number	Cycle 1					All Cycles				
	WBC	ANC	Plt	Hgb	Inf	WBC	ANC	Plt	Hgb	Inf
1	3	4	3	3	0	3	4	3	3	0
2	1	2	0	1	0	2	3	3	3	0
3	1	0	0	1	0	2	0	3	3	0
4	1	1	0	1	0	2	3	1	2	0
5	1	0	0	1	0	2	3	2	2	0
6	1	4	0	1	0	2	4	4	2	0
7	0	0	0	1	0	2	3	4	4	0
8	2	0	1	1	0	2	4	4	3	3
9	4	4	4	3	3	4	4	4	3	3
10	1	3	4	1	0	2	3	4	2	2

Abbreviations: WBC, white blood cells; ANC, absolute neutrophil count; Plt, platelets; Hgb, hemoglobin; Inf, infection.

and patient #10 had a partial response. All patients have experienced progressive disease, and the median time to progression was 9 months (range, 4–11 months). All patients have died, and the median survival time was 14 months (range, 7–19 months).

3.2. Pharmacokinetics

We evaluated apparent oral clearance because it was not dose-dependent over the small dose ranges for topotecan and etoposide in this study and because clearance might reveal major pharmacokinetic interactions between the two drugs. Complete pharmacokinetic data for topotecan were available for cycle 1 in eight patients, for cycle 2 in six patients, and for cycle 3 in five patients. Median (range) topotecan clearance values for cycles 1, 2, and 3 were 41 (20–55), 45 (25–65), and 48 (39–63) l/h, respectively. For etoposide, complete pharmacokinetic data were available for cycle 1 in nine patients, for cycle 2 in five patients, and for cycle 3 in six patients. Median (range) etoposide clearance values for cycles 1, 2, and 3 were 3.3 (1.0–5.4), 2.9 (0.8–3.9), and 2.8 (1.8–3.8) l/h, respectively.

4. Discussion

Greco [44] reviewed why topotecan should be considered for first-line therapy of SCLC. First, topotecan has a novel mechanism of action and demonstrated in vitro synergy with other agents that are active in SCLC. Second, there appears to be a lack of cross resistance between topotecan and other agents. Third, topotecan penetrates the blood-brain barrier and is active against brain metastases, which is a considerable problem in patients with SCLC. Fourth, although myelosuppression is the main toxicity, it is non-cumulative and manageable with hematologic growth factor support. Non-hematologic toxicities of topotecan are usually mild.

The maximum tolerated dose for oral topotecan as a single agent is 2.3 mg/m²/day for 5 days every 21 days. When combined with other cytotoxic drugs the topotecan dose has to be lower [44]. For instance, de Jonge et al. recommended topotecan 2 mg/m²/day p.o. for 5 days in combination with cisplatin 75 mg/m² i.v. on day 5 [11]. Pertinent to our study,

Shifflett et al. [12] and Gillenwater et al. [13] investigated the same 3-drug combination of topotecan on days 1–5, carboplatin on day 1, and etoposide on days 6–8. Due to dose-limiting hematologic toxicity, they changed the regimen to topotecan on days 1–3, carboplatin on day 3, and etoposide on days 4–6. Topotecan was dosed to a target area under the curve (AUC). They administered carboplatin at an AUC of 5 and etoposide orally at 100 mg/m²/day for 3 days. They also reported hematologic toxicity (neutropenia, thrombocytopenia, and anemia) to be dose-limiting. Thus their results are similar to ours, although they did not specify a topotecan dose.

The pharmacologic rationale of sequencing topotecan and etoposide plus cisplatin to overcome topoisomerase I and II resistance was also recognized by Aisner et al. [45]. Because of dose-limiting neutropenia, filgrastim was added similar to our regimen. Their recommended doses were topotecan 0.75 mg/m²/day days 1–3 i.v. over 30 minutes, cisplatin 20 mg/m²/day days 8–10 i.v. over 60 min, and etoposide 70 mg/m²/day days 8–10 i.v. over 60 min followed by filgrastim 5 μg/kg s.c. starting on day 11. The oral formulation of topotecan used in our trial has a bioavailability of 32–44% [19]. The median body surface area of our 10 patients was 1.86 m². It is therefore possible to estimate the total bioavailable topotecan dose on dose level 2 in our trial (3 mg × 5 days/1.86 m² × 32% = 2.58 mg/m²) which is comparable to the total dose administered by Aisner et al. (2.25 mg/m²). The bioavailability of oral etoposide is 50–75% [46–49]. The estimated total bioavailable dose of etoposide on dose level 2 (150 mg × 5 days ÷ 1.86 m² × 50% = 202 mg/m²) is also comparable to the total dose administered by Aisner et al. (210 mg/m²). Similar to our trial, Aisner et al. reported neutropenia lasting over 5 days and febrile neutropenia to be the dose-limiting toxicities [45]. Fifteen patients with solid tumors were accrued in that trial, and 7 of 12 evaluable patients achieved stable disease for ≥2 months (5 progressed).

Oral chemotherapy represents a change in contemporary oncology practice, driven by pharmacoeconomic issues, patient convenience, and the potential for improved quality of life [50]. Protracted schedules of drug administration in particular benefit from the availability of an oral

formulation. Both, topotecan and etoposide, are typically given over 3–5 days in clinical practice. The regimen developed by Aisner et al. [45] requires 6 clinic visits for drug administration per treatment cycle. Only carboplatin is infused in the clinic in our regimen. This is also an improvement over an earlier regimen that used continuous infusion of topotecan over 7 days with similar toxicity and efficacy [51].

The clearance values for topotecan and etoposide observed in this study are well within the published experience for both drugs [46–49]. Although the number of observations is small, no major pharmacokinetic interaction between topotecan and etoposide was apparent.

5. Conclusions

Neutropenia and thrombocytopenia were dose-limiting. The MTD is topotecan 3 mg/day p.o. days 1–5, carboplatin AUC 5 i.v. day 6, and etoposide 150 mg/day p.o. days 6–10 with filgrastim.

Conflict of interest statement

None declared.

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