

Phase II Study of Carboplatin, Irinotecan, and Thalidomide in Patients with Advanced Non-small Cell Lung Cancer

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Background: We hypothesized that thalidomide would improve the response and toxicity profile of chemotherapy with carboplatin and irinotecan.

Methods: The key eligibility criteria were stage IIIB (malignant pleural effusion) and IV non-small cell lung cancer, measurable disease, no prior chemotherapy, prior radiation only for brain metastasis, performance status 0 or 1, and adequate hematologic, hepatic, and renal function. Treatment consisted of carboplatin at a calculated area under the curve of 5 and infused intravenously for 30 min on day 1 and irinotecan (50 mg/m² intravenously for 90 min on days 1 and 8 every 21 days). Thalidomide was given orally every evening starting on day 1 until progressive disease; the starting dose was 200 mg per day, which was escalated by 100 mg per week if tolerated (maximum 1000 mg per day). The objectives were to determine the response rate, time to progression, overall survival, and toxicity profile.

Results: In all, 46 patients were enrolled, but three who never received protocol treatment were excluded from the analysis. The characteristics of the 43 eligible and treated patients included median age 63 (47–79), female/male 13/30, black/white 3/40, PS 0/1 in 10/33, and stage 3/4 in 6/37. The objective response rates were complete response 1 (2%), partial response 5 (12%), stable disease 24 (56%), progressive disease 9 (21%), and unevaluable for response 4 (9%). The median time to progression was 3.7 months (95% confidence interval [CI], 2.5–4.9). The median survival time was 8.1 months (95% CI, 5.0–12.9). Frequent toxicities were neutropenia, fatigue/malaise, and nausea/vomiting. Diarrhea was uncommon and mild.

Conclusions: This treatment regimen of carboplatin, irinotecan, and thalidomide was tolerable, with reversible neutropenia as the major toxicity and only minor diarrhea. The overall response rate did not meet our predetermined level of efficacy to merit further investigation.

Key Words: Phase II, Carboplatin, Irinotecan, Thalidomide, Non-small cell lung cancer.

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Lung cancer is the leading cause of cancer deaths in both males and females in the United States.¹ Approximately 15 to 20% of the patients have small cell lung cancer (SCLC), and 80 to 85% have non-small cell lung cancer (NSCLC).² Most patients present with stage III or IV disease. In the treatment of advanced NSCLC, survival is improved by chemotherapy compared with best supportive care, but the survival benefit is modest, and no particular two-drug combination is superior. For instance, the Eastern Cooperative Oncology Group (ECOG) compared cisplatin/gemcitabine, cisplatin/docetaxel, and carboplatin/paclitaxel against a reference regimen of cisplatin/paclitaxel in a large randomized phase III trial, and none of the newer doublets showed significant improvement in the median survival, which was approximately 8 months.³

Irinotecan has emerged as another active agent in advanced NSCLC.⁴ It is thought to have nonoverlapping toxicities with other drugs (i.e., carboplatin and paclitaxel).⁵ In a phase I study of irinotecan and carboplatin in previously untreated solid tumors that included advanced lung cancer, dose-limiting diarrhea, leukopenia/neutropenia, and thrombocytopenia were observed at carboplatin area under the curve (AUC) of 5 on day 1 and irinotecan 60 mg/m² on days 1, 8, and 15.⁶ The recommended phase II doses were carboplatin AUC of 5 and irinotecan 50 mg/m².⁶ In a phase II study of the combination of carboplatin AUC of 5 and irinotecan 50 mg/m² days 1, 8, and 15, 36 patients with measurable advanced NSCLC were treated.⁷ The results included a response rate of 25% (95% confidence interval [CI], 12–42%), a median survival of 10.8 months, and a 1-year survival rate of 38.9%, with major toxicities consisting of neutropenia, thrombocytopenia, anemia, nausea/vomiting, and diarrhea.⁷ Irinotecan was not given on days 8 or 15 if the leukocyte count was <3,000/ μ l or if the platelet count was <100,000/ μ l, or if diarrhea of at least grade 1 was present. The actual doses of irinotecan relative to the projected doses on days 8 and 15 were noted as 0.86 and 0.43, respectively.⁷ Because fewer than half of the patients could receive the dose of irinotecan on day 15 of the 28-day cycle, the authors suggested that the treatment schedule should be revised.⁷ This

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led us to investigate a 21-day cycle of carboplatin at an AUC of 5 on day 1 and irinotecan 50 mg/m² on days 1 and 8.

Thalidomide has diverse effects that include antiangiogenic, antineoplastic, and antiinflammatory actions. It is thought to inhibit angiogenesis by interfering with basic fibroblast growth factor and vascular endothelial growth factor.⁸⁻¹¹ Thalidomide also inhibits tumor necrosis factor- α production, which may result in diminished cancer cachexia.^{12,13} In a pilot study assessing the safety of thalidomide in combination with standard doses of paclitaxel and carboplatin in patients with advanced NSCLC, nine patients received paclitaxel 225 mg/m² for 3 hours and carboplatin AUC of 6 with thalidomide at a starting dose of 200 mg per day.¹⁴ The thalidomide dose was escalated by 200 mg per week to a target dose of 1000 mg per day if tolerated; thalidomide could continue for up to 6 months. The most frequent side effects were fatigue, constipation, nausea, myalgia, sensory neuropathy, and myelosuppression. Sixteen of 17 episodes of grade 3 or 4 hematologic toxicity occurred in five patients who had received prior chemotherapy. In previously untreated patients, the drug combination was well tolerated. The median tolerated dose of thalidomide was 600 mg per day. One patient with stage IIIA disease had a partial response, and one patient with stage IV disease had stable disease for more than 187 days.¹⁴

Irinotecan causes diarrhea and thalidomide causes constipation. Govindarajan et al. observed a striking absence of gastrointestinal side effects, especially diarrhea and nausea, when irinotecan and thalidomide were combined.¹⁵ The pathophysiological basis for this observation is unclear, but tumor necrosis factor- α inhibition by thalidomide may be implicated in this effect. Thalidomide also has known immunotherapeutic properties against inflammatory bowel disease.¹⁶

Our hypothesis was that thalidomide might improve the response and toxicity profile of carboplatin/irinotecan for three reasons: a) thalidomide has a novel mechanism of action that is different from classic cytotoxic drugs,⁸ b) it has already been successfully combined with carboplatin/paclitaxel with promising results in advanced NSCLC,¹⁴ and c) it has been observed that thalidomide decreases the gastrointestinal side effects of irinotecan.¹⁵ This phase II study investigated the combination of carboplatin, irinotecan, and thalidomide with the following objectives: a) to assess the response rate (primary objective), b) to estimate the time to progression and the overall survival duration, and c) to evaluate the toxicity profile.

PATIENTS AND METHODS

Patient Eligibility

All patients had histologically or cytologically documented NSCLC with either stage IIIB (because of malignant pleural effusion) or stage IV disease. All patients had to have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) by the National Cancer Institute. The eligibility criteria included age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, no prior chemotherapy, and no prior radiation except for brain metastasis. The required laboratory values at entry were absolute neutrophil count (ANC) $\geq 1,500/\mu\text{l}$,

platelet count $\geq 100,000/\mu\text{l}$, serum creatinine ≤ 1.5 mg/dl, total bilirubin ≤ 1.5 mg/dl, and pregnancy test negative for women of childbearing potential. Females who were pregnant or nursing were not eligible. Each patient had to give written informed consent after being informed of the research nature of the study and had to agree to use approved methods of birth control (i.e., two methods of birth control for women, and condoms for men).

Treatment Plan

Carboplatin was dosed at a calculated AUC of 5 and infused intravenously for 30 minutes on day 1. Irinotecan at a dose of 50 mg/m² was infused intravenously for 90 minutes on days 1 and 8. One cycle of chemotherapy with carboplatin/irinotecan was 21 days in length, and up to six cycles were administered. Premedication with ondansetron, granisetron, or palonosetron in combination with dexamethasone was standard. Ancillary medications were atropine for acute diarrhea from irinotecan and loperamide for delayed diarrhea. Thalidomide was given orally every evening from day 1 until disease progression. The starting dose was 200 mg. The thalidomide dose was escalated by 100 mg every week as tolerated to a maximum dose of 1000 mg. Thalidomide was continued until progressive disease was observed. The prolonged use of thalidomide was based on the assumption by Folkman that the antiangiogenic effect is slower than the cytotoxic effect of chemotherapy.¹⁷ Because thalidomide can cause severe birth defects in humans, women of childbearing potential were informed of the risks and agreed not to become pregnant while taking thalidomide. They were instructed to use effective contraception methods during their participation in the study. Patients who initially presented with brain metastases were allowed to receive whole-brain irradiation, but they had to be neurologically stable and off steroids before entering this trial. Patients who subsequently developed brain metastases were considered to have progressive disease. Palliative radiation therapy to other sites was not permitted. Patients with disease progression after a minimum of two cycles of carboplatin and irinotecan and patients with unacceptable toxicity were removed from protocol treatment. After patients were removed from this protocol, radiotherapy and second-line chemotherapy were allowed.

On day 1 of subsequent cycles, treatment was held for ANC $< 1,500/\mu\text{l}$ or platelets $< 100,000/\mu\text{l}$. If febrile neutropenia (defined as temperature $\geq 38.3^\circ\text{C}$ or 100.5°F concomitant with an ANC $< 500/\mu\text{l}$), neutropenic sepsis, or a platelet nadir of $< 25,000/\mu\text{l}$ developed in a given cycle, all subsequent cycles were given using 75% of carboplatin and irinotecan. If febrile neutropenia or platelet nadir $< 25,000/\mu\text{l}$ occurred despite this dose reduction, then 50% was given in the next and all subsequent cycles. If febrile neutropenia or platelet nadir $< 25,000/\mu\text{l}$ occurred on a subsequent cycle despite this second dose reduction, protocol therapy was discontinued. The use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor was discouraged but allowed if adverse prognostic factors existed.¹⁸ On day 8 of a treatment cycle, 100% of the irinotecan dose was given in cases of ANC $\geq 1,500/\mu\text{l}$ and platelets $\geq 100,000/\mu\text{l}$, and 75% was given in cases of ANC 1,000 to 1,499/ μl or platelets 75,000 to 99,999/ μl . In cases of

ANC $<1000/\mu\text{l}$ or platelets $<75,000/\mu\text{l}$ on day 8, treatment was held and restarted on day 1 of the following cycle at 100% if counts recovered to ANC $\geq 1,500/\mu\text{l}$ and platelets $\geq 100,000/\mu\text{l}$. If treatment had to be held for longer than 3 weeks, the patient was removed from the protocol. For grade 3 nonhematological toxicities, treatment was held until toxicity had improved to grade 1 or less, and treatment was continued at 75% dosage except for hepatic or neurotoxicity, in which cases it was continued at 50%. For grade 4 nonhematological toxicities, treatment was held until toxicity improved to grade 1 or less, and treatment was continued at 50% dosage except for hepatic or neurotoxicity, in which cases treatment was discontinued.

Clinical Evaluation

Prior to enrollment in the study and before each treatment cycle, patients had a comprehensive history and physical examination (including performance status), complete blood counts and differential, and serum chemistries (electrolytes, liver and kidney functions). Albumin, thyroid-stimulating hormone, lactate dehydrogenase, and pregnancy tests were performed before treatment and as indicated. Blood counts were repeated weekly. Staging studies included chest x-ray, CT of the chest and abdomen, bone scan, and CT or MRI of the brain. Restaging was performed every two cycles on carboplatin/irinotecan and then at least every 3 months until documentation of tumor progression while on thalidomide. The NCI RECIST criteria were used,¹⁹ and the NCI Common Toxicity Criteria (version 2.0) were in effect when this trial was activated.

Statistical Analyses

The optimal minimax two-stage phase II design proposed by Simon²⁰ was used to test the null hypothesis that the objective response was $\leq 25\%$ versus the alternative hypothesis that the response rate was $\geq 40\%$ with type I and II errors of 10%. The study was prospectively designed to initially accrue 39 evaluable patients. If nine or fewer of the first 39 evaluable patients responded to therapy, the study was to be terminated and the null hypothesis "accepted." However, if 10 or more responded, an additional 25 patients were to be accrued. It was expected that up to 10% of all patients would be ineligible or unevaluable; therefore, the overall study size was expected to be at least 43 and up to 70 patients. The response rate was estimated by dividing the number of complete and partial responses by the number of eligible treated patients. CIs were calculated based on the exact binomial distribution. Progression-free survival was defined as the time from protocol registration until disease progression or death. Survival was defined as the time from registration until death or the last date of contact. Kaplan-Meier methods were used to estimate the time to progression and survival distributions.

RESULTS

Forty-six patients were accrued in the study between November 2001 and September 2004. Three patients did not receive any protocol therapy and have been excluded from the analysis. The characteristics of the 43 eligible treated patients are shown in Table 1.

TABLE 1. Patient characteristics ($n = 43$)

Age	
Median (range)	63 (47–79)
≥ 60 yr	27 (63%)
Sex	
Female	13 (30%)
Male	30 (70%)
Race	
Black	3 (7%)
White	40 (93%)
Performance status	
0	10 (23%)
1	33 (77%)
Histology	
Adenocarcinoma	18
Squamous cell carcinoma	10
Large cell carcinoma	4
Undifferentiated nonsmall carcinoma	11
Stage	
IIIB	6 (14%)
IV	37 (86%)
Prior treatment	
Chemotherapy	0 (0%)
Radiotherapy	5 (12%)

At least two cycles of carboplatin and irinotecan were administered in 39 patients. The median number of cycles was four. Sixteen patients received all six cycles of carboplatin and irinotecan. One patient is alive without tumor progression at 30 months, and three patients are alive with progressive disease. The median dose of thalidomide was 400 mg daily (range, 200–800 mg). One patient was able to tolerate 600 mg of thalidomide daily for 30 months. Table 2 summarizes the response to treatment. Two patients died within 30 days of registration of their progressive lung cancer. Two other patients refused further therapy after one cycle of treatment and thus could not be evaluated for tumor response. Based on all 43 eligible treated patients, the objective response rate was 14% (95% CI, 5–28%).

Thalidomide was given until tumor progression. The median time to progression was 3.7 months (95% CI, 2.5–4.9 months). Thirty-nine of the 43 patients have died. The median survival time was 8.1 months (95% CI, 5.0–12.9 months). Progression-free survival and overall survival are graphically depicted in Figure 1. The estimated 1-year survival rate was 37%.

TABLE 2. Objective response in 43 patients

Complete response	1 (2%)
Partial response	5 (12%)
Stable disease	24 (56%)
Progressive disease	9 (21%)
Early death (within 30 days of registration)	2 (5%)
Unevaluable (patient refusal)	2 (5%)
Overall response rate	6 (14%)
95% confidence interval	5–28%

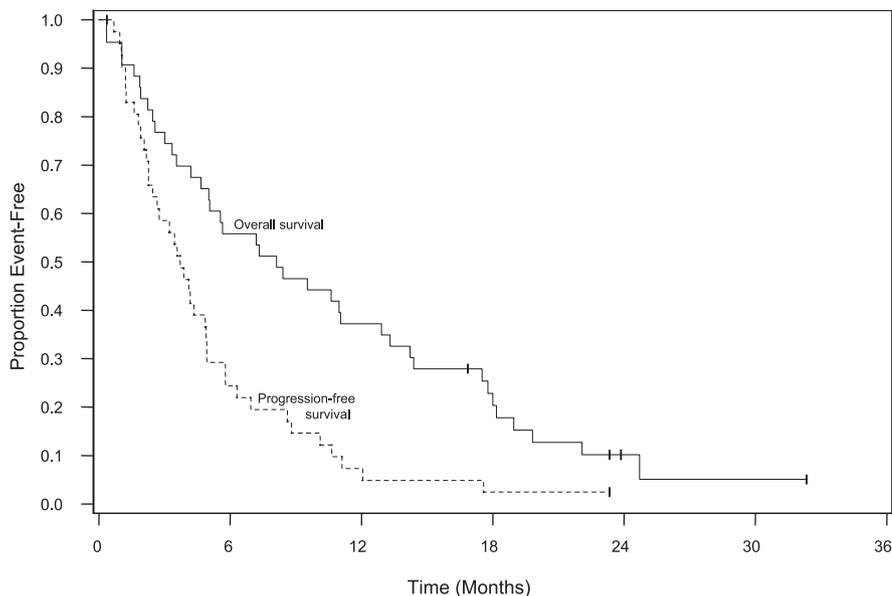


FIGURE 1. Progression-free and overall survival.

Table 3 summarizes the adverse events experienced by the 43 patients treated on protocol. The most common toxicity was reversible neutropenia. Although grade 3 and 4 neutropenia occurred in 16 patients (37%), neutropenic fever was only observed in one patient (2%). Thrombocytopenia was also encountered (Table 3) but did not require platelet transfusion. Diarrhea was not a serious problem. No cases of uncontrolled hypertension or serious hemorrhage such as hemoptysis were observed. No grade 5 adverse events were encountered.

DISCUSSION

This study was prospectively designed with a primary objective of distinguishing between objective response rates of 25 versus 40% as stated in the statistical section. When 39 patients could be evaluated for tumor response but only six responded (Table 2), the study was closed as planned. Our conclusions are that this treatment regimen of carboplatin,

irinotecan, and thalidomide was tolerable, with reversible neutropenia as the major toxicity. Diarrhea was an infrequent toxicity, which was consistent with the hypothesis that thalidomide would counteract the diarrhea from irinotecan. However, the overall response rate did not meet our predetermined level of efficacy to merit further investigation.

In the large phase III study by ECOG, the response rate for all 1155 eligible patients was 19%, with a median survival of 7.9 months (95% CI, 7.3–8.5 months).³ These results may be used as a benchmark for platinum-based doublets with paclitaxel, docetaxel, or gemcitabine. Our much smaller phase II trial of carboplatin, irinotecan, and thalidomide resulted in a response rate of only 14%, yet the median survival was 8.1 months (95% CI, 5.0–12.9 months). Thus, we were unable to demonstrate an improvement with the addition of thalidomide to carboplatin and irinotecan. This does not preclude the possibility of benefit from adding thalidomide to a different regimen of chemotherapy. Our failure to show a benefit for thalidomide also does not invalidate antiangiogenesis as a valid treatment strategy for lung cancer.

Antiangiogenic monoclonal antibodies have recently been developed for the treatment of NSCLC as reviewed by Sandler.²¹ Indeed, 878 patients with stage IIIB (pleural or pericardial effusion) and stage IV nonsquamous NSCLC with a performance status of 0 or 1 were enrolled by ECOG contemporary to our trial (July 2001 to April 2004) to a randomized phase III trial of carboplatin/paclitaxel with and without bevacizumab.²² Carboplatin/paclitaxel/bevacizumab had a response rate of 27%, which was significantly ($p < 0.0001$) higher than the response rate of 10% for carboplatin/paclitaxel. Progression-free and overall survival estimates were also significantly superior for the bevacizumab-containing regimen: 6.4 versus 4.5 and 12.5 versus 10.2 months, respectively. This ECOG study is one of the very few examples in which the addition of a new drug to a platinum

TABLE 3. Adverse events of grade 3 and 4 severity with an incidence of $\geq 5\%$

Type of Event	Grade, n (%)	
	3	4
Blood/bone marrow		
Leukocytes	7 (16)	2 (5)
Neutrophils	11 (26)	5 (12)
Hemoglobin	2 (5)	0 (0)
Platelets	2 (5)	1 (2)
Gastrointestinal		
Diarrhea	2 (5)	1 (2)
Nausea	5 (12)	0 (0)
Vomiting	5 (12)	0 (0)
Constitutional		
Malaise/fatigue	7 (16)	1 (2)

doublet improved response rate and survival time in patients with NSCLC.

Bevacizumab adds complexity to the treatment regimen compared with an oral drug such as thalidomide. On the other hand, a neurotoxic drug such as thalidomide may have problems with adherence compared with a parenteral drug like bevacizumab. Bevacizumab is not indicated in squamous cell lung cancer. Therefore, further investigations of drugs with novel molecular target such as VEGF are warranted.

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