Phase II Trial of Irinotecan, Paclitaxel and Carboplatin in Patients with Previously Untreated Stage IIIB/IV Nonsmall Cell Lung Carcinoma

Mark A. Socinski, M.D.[1]
Alan B. Sandler, M.D.[2]
Valerie K. Israel, M.D.[3]
Heidi H. Gillenwater, M.D.[1]
Langdon L. Miller, M.D.[4]
Paula K. Locker, M.S.[4]
Alessandro Antonellini, M.S.[4]
Gary L. Elfring, M.S.[4]
Ronald B. Natale, M.D.[5]

[1] Multidisciplinary Thoracic Oncology Program, University of North Carolina, Chapel Hill, North Carolina.

[2] Division of Hematology/Oncology, Vanderbilt University, Nashville, Tennessee.

[3] Synergy Hematology/Oncology Medical Associates, Los Angeles, California.

[4] Pharmacia Corporation, Peapack, New Jersey.

[5] Cedars-Sinai Medical Center, Los Angeles, California.

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Address for reprints: Mark A. Socinski, M.D., Director, Multidisciplinary Thoracic Oncology Program, University of North Carolina at Chapel Hill, 3009 Old Clinic Bldg, CB # 7305, Chapel Hill, NC 27599; Fax: 919-966-6735; E-mail: socinski@med.unc.edu

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BACKGROUND. This Phase II multicenter, open-label, single-arm study evaluated the efficacy and safety of a three-drug combination of irinotecan (CPT-11), paclitaxel, and carboplatin in advanced nonsmall cell lung carcinoma (NSCLC).

METHODS. Patients received repeated 21-day cycles at starting doses of paclitaxel 175 mg/m^2 administered over 3 hours, followed by carboplatin AUC of 5 over 30 minutes and CPT-11 at a starting dose level of 100 mg/m^2 over 90 minutes, all given on the first day of each cycle. Patients were evaluated for objective tumor response, time to tumor progression (TTP), survival, and safety.

RESULTS. Forty patients were enrolled. Baseline patient characteristics included: median age 58 years (range, 32–79); 23 males and 17 females; performance status of 0 (21 patients), 1 (18 patients), or 2 (1 patient); and Stage IIIB (10 patients) and Stage IV (30 patients) disease. A median of six cycles (range, one to eight) were administered. Grade 3–4 toxicities observed in $\geq$ 10% of the patients included neutropenia (78%), asthenia (20%), diarrhea (20%), nausea (18%), vomiting (13%), anemia (10%), and dyspnea (10%). Febrile neutropenia occurred in eight patients (20%), with one death due to neutropenic sepsis. Twelve of 38 evaluable patients had confirmed tumor responses (32%), while 21 (55%) had stable disease (including 12 patients [32%] with minor responses). Only 13% had disease progression at their initial tumor assessment. The median TTP and survival were 5.3 months (range, 0.03–6.2 months) and 12.5 months (range 0.3–28.6+ months), respectively. The one and two year survival probabilities were 0.50 (95% confidence interval [CI], 0.28–0.73) and 0.21 (95% CI, 0.0–0.67), respectively.

CONCLUSIONS. The combination of CPT-11, paclitaxel, and carboplatin can be safely administered and is active in the treatment of advanced NSCLC. Based on the favorable survival outcome, this regimen is undergoing evaluation in prospective randomized trials. ***Cancer* 2002;95:1520–7.** © *2002 American Cancer Society.*
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KEYWORDS: nonsmall cell lung carcinoma, chemotherapy, paclitaxel, carboplatin, irinotecan.

Lung carcinoma remains the leading cause of cancer death in the United States.[1] In 2001, approximately 169,500 new cases and 157,400 deaths from this disease are expected.[1] Nonsmall cell lung carcinoma (NSCLC) accounts for 75–80% of all lung cancers. Most patients (70%) with newly diagnosed NSCLC have locally advanced (Stage IIIB) or metastatic disease (Stage IV) at the time of diagnosis.[2] For patients with a good performance status, systemic treatment is the standard of care.[3] Platinum-based, two-drug chemotherapy regimens clearly prolong survival and palliate symptoms in this population.[4–8] However, median survival with such regimens remains 8–10

months, and 1-year survival rates are 30–40%.[9] Clearly new strategies are required to make further therapeutic gains in this disease setting.

The combination of carboplatin and paclitaxel represents one of the current standards of care for advanced or metastatic NSCLC based on the results of several recent Phase III trials.[10–13] Dose-limiting toxicity (DLT) has consisted primarily of mild to moderate myalgia/arthralgias or cumulative sensory neuropathy, while myelosuppression has been modest. In general, carboplatin/paclitaxel has been associated with significantly lower rates of severe toxicity compared with cisplatin-based doublet regimens.[12,14] Given this toxicity profile, incorporation of a third active agent with carboplatin and paclitaxel was considered a strategy that could enhance therapeutic outcomes.

Irinotecan (CPT-11) is a water-soluble prodrug that is metabolized in vitro to an active cytotoxic metabolite, SN-38. SN-38 binds to topoisomerase I, an enzyme that relieves torsional strain in DNA during DNA replication or transcription, and stabilizes topoisomerase I in a complex with DNA. During cell division, DNA replication forks collide with these enzyme-DNA complexes, resulting in double-stranded DNA breaks and subsequent programmed cell death.[15,16] CPT-11 alone or in combination with cisplatin has significant activity in NSCLC.[17–25] The combination of CPT-11 and cisplatin represents the standard of care in Japan based on Phase III trials conducted in that country.[26,27]

We have previously reported a Phase I trial that combined escalating doses of CPT-11 with fixed doses of carboplatin and paclitaxel in 33 patients with advanced NSCLC.[28] The primary DLT of this regimen was diarrhea and neutropenia. Starting doses suitable for Phase II study were defined as paclitaxel 175 mg/m^2 over three hours, carboplatin AUC 5, and CPT-11 100 mg/m^2, all given on Day 1 every 21 days. The confirmed response rate was 39%, the median survival was 11.0 months, and the one-year survival was 46%. Given these favorable outcomes in the Phase I setting, the current Phase II study was conducted in patients with advanced NSCLC to further define the efficacy and safety of this three-drug combination.

PATIENTS AND METHODS

Patient Selection

Adult patients were enrolled in the study if they had a histologic or cytologic diagnosis of NSCLC. Patients could have Stage IIIB disease with malignant pleural/pericardial effusions or supraclavicular adenopathy, Stage IV disease, or recurrent disease that was Stage IIIB or IV upon restaging following surgery. Patients were also required to have a performance status of 0, 1, or 2 on the Southwest Oncology Group scale; a predicted life expectancy of $\geq$ 12 weeks; measurable disease in at least one area which had not been subject to prior irradiation; no prior chemotherapy; completion of any previous radiation therapy $\geq$ 3 weeks prior to enrollment; and successful surgical or radiotherapeutic control of any brain metastases. Organ function requirements included: a white blood count $\geq$ 3.5 $\times$ 10^9/L, an absolute neutrophil count $\geq$ 1.5 $\times$ 10^9/L, platelet count $\geq$ 100 $\times$ 10^9/L, hemoglobin $\geq$ 9 g/dL, total serum bilirubin $\leq$ 1.25 the institutional upper limit of normal (IULN), hepatic transaminase $<$ 3 $\times$ IULN, and a calculated creatinine clearance of $\geq$ 50 mL/minute.[29]

Patients were not eligible for study enrollment if they had any of the following: active or uncontrolled infection; significant cardiovascular disease (uncontrolled hypertension, unstable angina, active congestive heart failure, myocardial infarction within the previous year, uncontrolled serious arrhythmia); prior malignancies, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical carcinoma or other cancer for which the patient had been disease-free for five years; evidence of peripheral neuropathy; a history of seizures or use of phenytoin or phenobarbital prophylaxis; pneumonitis or uncontrolled large pleural effusions; uncontrolled diabetes mellitus; or pregnancy, lactation, or refusal to use effective contraception.

All study candidates were required to provide written informed consent as approved by local institutional review boards before initiation of any study procedures.

Treatment Plan

Paclitaxel and carboplatin (Bristol-Myers Squibb, Inc., Princeton, NJ) were obtained commercially. Paclitaxel was given as an intravenous infusion at 175 mg/m^2 over three hours, followed by carboplatin (AUC of 5)[30] intravenously over 30 minutes. Following carboplatin, CPT-11 (Pharmacia Corp., Peapack, NJ) was infused intravenously at 100 mg/m^2 over 90 minutes. All three drugs were given on Day 1 of a 21-day cycle. Treatment continued at planned intervals of three weeks for six cycles or until patients had disease progression, developed unacceptable drug toxicity not responding to dosage modification or supportive therapy, or withdrew consent. Continuing treatment beyond six cycles was done at the discretion of the treating physician.

Prevention of paclitaxel reactions consisted of dexamethasone (20 mg orally) on the evening prior to chemotherapy and again on the morning of treatment and intravenous diphenhydramine (50 mg) and either

TABLE 1
Dose Modifications for the Next Cycle of Therapy Based on the Worst Toxicity in the Preceding Cycle

NCI toxicity grade	Drug	Adverse Event				
		Neutrophils	Platelets	Neurosensory	AST[c]/bilirubin	Diarrhea
0-1	Paclitaxel	None	None	None	None	None
	Carboplatin	None	None	None	None	None
	CPT-11	None	None	None	None	None
2	Paclitaxel	None	None	None	↓ 25 mg/m^2	None
	Carboplatin	None	None	None	None	None
	CPT-11	None	None	None	None	None
3	Paclitaxel	None	None	↓ 25 mg/m^2	↓ 50 mg/m^2	None
	Carboplatin	None	None	None	None	None
	CPT-11	None	None	None	↓ 20 mg/m^2	None
4	Paclitaxel	None	None	NA[a]	Omit Dose	None
	Carboplatin	↓ 1 AUC[b]	↓ 1 AUC	NA[a]	None	None
	CPT-11	↓ 20 mg/m^2[b]	None	NA[a]	↓ 20 mg/m^2	↓ 20 mg/m^2

[a] NA: not applicable because there were no Grade 4 CTC criteria for neurosensory or arthralgia/myalgia events.

[b] Carboplatin dose was decreased for first cycle in which Grade 4 neutropenia or neutropenic fever occurred. CPT-11 dose was decreased only if Grade 4 neutropenia or neutropenic fever occurred after decrease of carboplatin dose in the previous cycle.

[c] Serum glutamic oxaloacetic transaminase.

NCI: National Cancer Institute; CTC: Common Toxicity Criteria.

cimetidine (300 mg) or ranitidine (50 mg) 30 minutes prior to paclitaxel. Cholinergic symptoms occurring during or shortly after receiving CPT-11 could be treated with intravenous or subcutaneous atropine (0.25–1 mg).[31,32] Intravenous administration of dexamethasone (10 mg), either ondansetron (32 mg) or granisetron (10 ug/kg), and lorazepam (1–2 mg) were suggested as components of the pretreatment antiemetic regimen. Oral dexamethasone (4 mg every 12 hours for 8 doses) was used prophylactically if ≥ Grade 2 arthralgias/myalgias occurred, with the addition of ibuprofen (600-800 mg four times per day) as needed. Patients were instructed to begin taking loperamide at the first sign of diarrhea that occurred ≥ 12 hours following CPT-11 administration. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not allowed.

Dose Modifications for Toxicity

Toxicities were graded using the National Cancer Institute Common Toxicity Criteria, Version 1.0. As described in Table 1, doses of chemotherapy in subsequent cycles of treatment were to be adjusted according to the type and severity of toxicity observed in the prior cycle. Initiation of a subsequent cycle of chemotherapy was delayed until patients achieved an absolute neutrophil count ≥ 1.5×10^9/L and platelet count ≥ 100×10^9/L and had resolution of nonhematologic toxicities to ≥ Grade 1.

Patient Evaluation

Prior to treatment, patients underwent medical history and physical examination, electrocardiogram, laboratory evaluation (complete blood count, serum chemistries, and pregnancy testing for women of childbearing potential), and baseline tumor measurements. The medical history, physical examination, and serum chemistries were repeated prior to each three-week cycle. Complete blood counts and assessments of adverse events were obtained weekly throughout treatment. Patients were to have on-study tumor evaluations every six weeks.

Tumor response was assessed according to modified World Health Organization criteria (i.e., measurable disease, evaluable disease, nonevaluable disease; complete response, partial response, stable disease [including the subset of minor responses, comprising ≥ 25% but <50% reduction in tumor area], and progressive disease).[33] Tumors were reassessed during treatment using the same imaging method used to establish baseline tumor measurement. Previously irradiated lesions were excluded from evaluation for tumor response. Whenever possible, patients with evidence of tumor response were to have confirmation within four to six weeks after the initial documentation of response. In addition, time to response, duration of response, time to tumor progression, and survival were determined.

Statistics

Patient characteristics, treatment administration, the safety profile of the combination, and response rate by

TABLE 2
Baseline Patient Characteristics

Parameter	*n* = 40
Median age, years [range]	58 [32–79]
Gender (%)	
Male	23 (58)
Female	17 (42)
Baseline performance status (%)	
0	21 (52)
1	18 (45)
2	1 (3)
Stage, n (%)	
IIIB	10 (25)
IV	30 (75)
Prior treatment, n (%)	
Surgical resection	11 (28)
Radiotherapy	8 (20)
Number of measured metastatic sites[a] (%)	
1	20 (50)
2	15 (38)
> 2	4 (10)
Common sites of measurable disease[a] (%)	
Lung	33 (83)
Lymph nodes	16 (40)
Liver	7 (18)
Adrenal	4 (10)
Soft tissue	1 (3)
Renal	1 (3)

[a] Includes 39 patients with measurable disease at baseline.

TABLE 3
Adverse Events

	NCI CTC grade, *n* (% of patients)		
Parameter	2	3	4
Hematologic			
Leukopenia	13 (33)	14 (35)	10 (25)
Neutropenia	5 (13)	10 (25)	21 (53)
Anemia	21 (53)	2 (5)	2 (5)
Thrombocytopenia	1 (3)	2 (5)	1 (3)
Nonhematologic			
Alopecia	23 (58)	NA[a]	NA[a]
Asthenia	13 (33)	8 (20)	NA[a]
Nausea	9 (23)	7 (18)	NA[a]
Diarrhea	6 (15)	4 (10)	4 (10)
Vomiting	6 (15)	4 (10)	1 (3)
Arthralgia	6 (15)	1 (3)	0
Myalgia	6 (15)	1 (3)	0
Dyspnea	6 (15)	2 (5)	2 (5)
Neuropathy	4 (10)	1 (3)	0
Dehydration	3 (8)	2 (5)	1 (3)

[a] NA: not applicable because there were no Grade 4 CTC criteria for these events.
NCI: National Cancer Institute; CTC: Common Toxicity Criteria.

baseline patient characteristics were characterized using descriptive statistics. The 95% confidence intervals (CI) for the estimated response rates were calculated using the binomial distribution. Time-to-event probability curves and the probability of survival at one and two years were estimated using Kaplan-Meier methods.

RESULTS

Patient Characteristics

A total of 40 patients were enrolled between February 1998 and March 1999. Followup information was collected through November 2000. All 40 patients were evaluable for toxicity while 38 were evaluable for tumor response. The characteristics of the patient population included in the current study are shown in Table 2. The median age was 58 years (range, 32–79) among the 23 men (58%) and 17 women (42%). Performance status was relatively good (0–1) for most patients; only one patient (3%) had a baseline performance status of 2. The majority of the patients (75%) had Stage IV disease. None of the patients had received prior chemotherapy. Eleven patients (28%) had undergone a previous surgical resection while 8 (20%) had received prior radiotherapy. Forty-eight percent of patients had two or more sites of measured metastatic disease, with the lung being the predominant site of measurable disease.

Treatment Administration

It was planned that, whenever possible, a minimum of six cycles of therapy was to be given to each patient. A total of 206 cycles of treatment were administered (median 6; range, 1–8). Twenty-five (62.5%) patients completed ≥ six cycles, with 22 patients receiving six cycles and 3 patients completing eight cycles. Twenty-eight (14%) treatment cycles were delayed by > three days due to toxicity, primarily because of neutropenia. The relative dose intensity (proportion of treatment delivered relative to planned treatment delivery over time) was 0.96 for paclitaxel, 0.88 for carboplatin, and 0.94 for CPT-11. The comparatively lower carboplatin relative dose intensity resulted from selective reductions in the dose of this drug at the first occurrence of Grade 4 myelosuppression.

Adverse Events

Table 3 shows both the hematologic and nonhematologic adverse events observed in the current trial. The predominant Grade 3-4 hematologic toxicity was neutropenia, observed in 78% of patients. Febrile neutropenia (defined as Grade 4 neutropenia with ≥ Grade 2 fever) occurred in eight patients (20%). There was one treatment-related death (2.5%) due to neutropenic sepsis. Grade 3–4 anemia and thrombocytopenia were

uncommon, occurring in only 10% and 8% of patients, respectively.

The most often observed Grade 3–4 nonhematologic toxicities were asthenia (20%), diarrhea (20%), nausea (18%), vomiting (13%), and dyspnea (10%). Other toxicities were uncommon, particularly the myalgia/arthralgia syndrome and neuropathy.

Tumor Response and Survival

Two of the 40 patients were not assessable for response. One patient died during Cycle 1 (neutropenic sepsis) and one patient had only evaluable disease. Among the 38 assessable patients, there were 16 (42%) patients who experienced a $\geq$ 50% reduction in tumor area during the study. In 12 of these patients, the response was confirmed $\geq$ four weeks later, resulting in a confirmed tumor response rate of 32% (95% CI, 18–49%). All the responses were partial. Twenty-one patients (55%) had stable disease; however, 12 of these 21 patients (32% of all patients) had a minor tumor response (defined as $\geq$ 25% but $<$ 50% reduction in total tumor area). Only 5 of 38 (13%) patients had progressive disease at the initial response assessment.

The median time to tumor response in the 12 patients who had confirmed objective responses was 1.3 months (range, 1.2–1.4 months), and the median response duration from the start of therapy was 6.2 months (range, 4.2–6.2). For all 40 patients, the median time to tumor progression was 5.3 months (range, 0.03–6.2 months). The median survival was 12.5 months (range 0.3–28.6+; 95%CI, 8.4–18.7 months). The one- and two- year survival probabilities were 0.50 (95%CI, 0.28–0.73) and 0.21 (95%CI, 0.0–0.67), respectively. A Kaplan-Meier survival curve for all 40 patients entered on the current trial is shown in Figure 1.

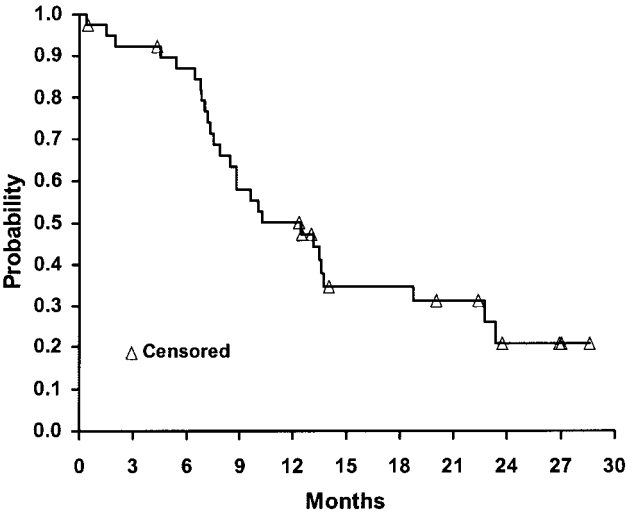

FIGURE 1. Kaplan–Meier survival curve (n = 40); Δ denotes censored values.

DISCUSSION

Platinum-based, two-drug combination chemotherapy regimens have become the standard of care in the palliative treatment of advanced Stage IIIB/IV NSCLC.[3,4,9] The survival gains associated with adding a new agent (paclitaxel, docetaxel, gemcitabine, or vinorelbine) to platinum are modest but real, with median survival times of approximately eight to nine months and one-year survival rates of 30-36% in recently completed Phase III trials.[4,10–12]

Unfortunately, a survival plateau has been reached in advanced NSCLC. In an attempt to improve therapeutic outcomes, the strategy of adding new active agents to standard platinum-based doublets has been considered. In the past, this strategy has not been successful, in part due to the low single-agent activity of available agents and the increasing risk of toxicity with the use of multi-drug, cisplatin-based therapies.[34,35] The development of carboplatin-based, two-drug regimens has improved the therapeutic index because carboplatin is associated with less toxicity but similar efficacy to that of cisplatin.[12] The combination of carboplatin and paclitaxel has been studied in several Phase III trials and represents a standard of care based on survival rates comparable to other regimens.[10–12] In general, carboplatin in combination with paclitaxel has been more tolerable in these Phase III trials,[10–12] making this doublet a suitable regimen with which to combine a new agent. One of these new agents is CPT-11, a topoisomerase I inhibitor. In addition to its single-agent activity,[17–21] preclinical data suggest either synergistic or additive cytotoxicity when CPT-11 is combined with platinum[36,37] or with paclitaxel.[38] These collective findings suggest that incorporation of CPT-11 into the combination of carboplatin and paclitaxel was a reasonable approach in an attempt to improve therapeutic outcomes in advanced NSCLC.

Our previous Phase I experience[28] with this three-drug regimen of CPT-11, paclitaxel, and carboplatin was sufficiently encouraging that we pursued the current Phase II trial. Reassuringly, the response and survival outcomes documented in the Phase I trial were confirmed in this Phase II trial (Table 4). Although the median and one-year survivals were favorable, one must be careful in interpreting Phase II trials, as patient selection may clearly bias the outcomes. Nevertheless, this was a multicenter trial, and the results with this triplet combination have been consistent across both Phase I and II trials. To place these results in context, Table 5 shows findings with other three-

TABLE 4
Efficacy Outcomes

Parameter	Phase I[a] *n* = 32	Phase II[b] *n* = 40
Confirmed response rate, %	39[c]	32[d]
Median TTP, months	6.8	5.3
Median survival, months	11.0	12.5
Survival probability		
one-year	.46	.50
two-year	.18	.21

[a] Reference 28.
[b] Current study.
[c] Twelve out of 31 evaluable patients.
[d] Twelve out of 38 evaluable patients.
TTP: time to progression.

drug combinations from Phase II trials conducted in the United States in which a recently developed agent has been added to the doublet of carboplatin and paclitaxel.[39–41] Two of these trials[39,41] were also multi-institutional. As is shown, our three-drug regimen compares favorably with these other triple combinations involving these other newer cytotoxics.

Other investigators have also incorporated CPT-11 into platinum-based doublets.[42–44] Fujita et al. have reported two Phase I trials adding CPT-11 to cisplatin and ifosfamide. Both trials used prophylactic G-CSF. In the first Phase I trial,[42] the doses of cisplatin (20 mg/m^2, Days 1-4) and ifosfamide (1.5 gm/m^2, Days 1-4) were fixed. CPT-11 was administered on Days 1, 8, and 15 of each cycle. The maximum tolerated dose of CPT-11 on this schedule with cisplatin and ifosfamide was 60 mg/m^2. In the second Phase I trial,[43] fixed doses of CPT-11 (60 mg/m^2, Days 1, 8, 15) and ifosfamide (1.5 gm/m^2, Days 1-4) were used. The cisplatin dose was escalated starting from 60 mg/m^2 on Day 1. A Phase II dose of 70 mg/m^2 of cisplatin was recommended. Lastly, Kiura et al.[44] incorporated escalating doses of CPT-11 on Day 2 and cisplatin (60-80 mg/m^2) on Day 1 with fixed doses of docetaxel (60 mg/m^2) on Day 1. The recommended doses of cisplatin and CPT-11 on Day 1 were 60 mg/m^2 each. This regimen also required use of prophylactic G-CSF. The DLTs reported in all three studies were neutropenia, thrombocytopenia, and diarrhea. These CPT-11-containing regimens were quite active, with reported response rates ranging from 52 to 66%, median survivals of 13 to 17 months, and 1-year survival rates of 54 to 56%.

Whether new three-drug combinations will definitely improve survival over two-drug combinations remains unclear. Only one trial involving the use of new agents in cisplatin-based triplet combinations has been published to our knowledge.[45] In that trial, cisplatin/vinorelbine/gemcitabine was compared with cisplatin/vinorelbine and with cisplatin/gemcitabine. Enrollment into the cisplatin/vinorelbine arm of the trial was stopped early because of inferior survival. The trial has continued accrual to the remaining two arms to discern if the three-drug combination provides longer survival relative to the cisplatin/gemcitabine regimen. Several other trials designed to address the benefits and risks of three-drug combinations versus standard two-drug combinations are ongoing.[46]

A concern in the development of three-drug regimens is the potential for excessive toxicity in this disease setting. The regimen described in this report was associated with a 78% rate of Grade 3-4 neutropenia. However, only 20% of patients developed fever/neutropenia. This is similar to the rates of febrile neutropenia seen with other modern three-drug regimens. Hainsworth et al. reported a 16% rate of febrile neutropenia with the combination of gemcitabine, carboplatin, and paclitaxel.[39] The same investigators reported a 36% rate of febrile neutropenia with the combination of vinorelbine, carboplatin, and paclitaxel.[41] Other significant hematologic toxicities with the current triple-drug regimen were uncommon. The predominant nonhematologic toxicity in the current study was diarrhea, with Grade 3–4 toxicity occurring in 20% of patients. Despite this, the majority of patients (62.5%) received six or more cycles of therapy and had a relative CPT-11 dose intensity of 0.94, suggesting that this regimen is tolerable and is not associated with cumulative toxicities. Although tolerable, routine use of three-drug regimens in patients with Stage IV disease should be restricted to patients with a good performance status and will only be justified in the long term if clinically significant improvements in survival are proven in well-designed Phase III trials.

In conclusion, the current multicenter Phase II trial documents that the three-drug combination of CPT-11, paclitaxel, and carboplatin is an efficacious and tolerable regimen in patients with advanced NSCLC and good baseline performance status. We believe continued evaluation of this regimen is indicated in patients with Stage IIIB/IV disease; randomized trials are ongoing. New trials should also evaluate patients with earlier stages of NSCLC for whom cure or long-term survival is possible. Other potential areas of evaluation might include malignancies in which all three components of this regimen are active, such as small cell lung carcinoma or cancers of the head and neck, esophagus, stomach, or ovary.

TABLE 5
New Cytotoxic Agents Added to Carboplatin and Paclitaxel in Advanced NSCLC

			Patient Characteristics		Efficacy outcomes		
Author	n	Therapeutic regimen	Stage IIIB %	Performance status 2%	Response rate %	Median survival (months)	One-year Survival Probability
Hainsworth[39]	77	Carboplatin AUC 5 D1 Paclitaxel 200 mg/m^2/1h D1 Gemcitabine 1000 mg/m^2 D1, 8	27	8	44	9.9	.47
Kelly[40]	50	Carboplatin AUC 5 D1 Paclitaxel 175 mg/m^2/3h D1 Gemcitabine 1000 mg/m^2 D1, 8	8	6	21	8.0	.33
Hainsworth[41]	89	Carboplatin AUC 6 D1 Paclitaxel 200 mg/m^2/1h D1 Vinorelbine 22.5 mg D1, 8 or 15	35	12	35	8.6	.43
Socinski[a]	40	Carboplatin AUC 5 D1 Paclitaxel 175 mg/m^2/3h D1 CPT-11 100 mg/m^2 D1	25	3	32	12.5	.50

[a] Current study.
NCSLC: non small cell lung carcinoma; D: day.

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