Weekly Irinotecan and Cisplatin in Advanced Non-Small Cell Lung Cancer: A Multicenter Phase II Study


ABSTRACT
The combination of weekly irinotecan (CPT-11) and monthly cisplatin has shown promising activity in advanced non-small cell lung cancer (NSCLC) in previous Phase I and II studies. However, same-day administration of these agents may better exploit their therapeutic synergy and minimize toxicities. This multicenter Phase II study was undertaken to evaluate the efficacy and safety of a combination of weekly CPT-11 and weekly cisplatin in patients with advanced NSCLC. Patients with chemotherapy-naive stage IIIIB or IV NSCLC were treated with repeated cycles of therapy comprising weekly treatment with both cisplatin and CPT-11 for 4 weeks, followed by a 2-week rest. The starting doses of CPT-11 and cisplatin were 65 and 30 mg/m², respectively. Treatment was continued until the occurrence of disease progression, unacceptable toxicity, or a maximum of six cycles. Fifty patients were enrolled. The median age was 59 years (range, 44–79 years). Eastern Cooperative Oncology Group performance status was 0 in 22 patients, 1 in 19 patients, and 2 in 9 patients. Seven and 43 patients had stages IIIIB and IV disease, respectively. Five patients had brain metastasis. Patients received a median of three 6-week cycles (range, 1–6). The objective response rate was 36% (18 of 50; 95% confidence interval, 24–54%) and included 18 partial responses. Median time to tumor progression was 6.9 months (range, 0.6–15.2). The median survival was 11.6 months (range, 0.16–21.9 months), and the 1-year survival rate was 46%. Grade 3/4 nonhematological toxicities included vomiting (12%) and diarrhea (26%). Grade 3/4 hematological toxicities included anemia (14%), neutropenia (26%), and thrombocytopenia (14%). Relative dose intensities for CPT-11 and cisplatin were 89 and 62%, respectively. Weekly combined administration of CPT-11 and cisplatin achieved a promising overall response rate, median time to tumor progression, and median survival in patients with stage IIIB/IV NSCLC. The regimen was well tolerated, and the planned dose intensity was well maintained. Further evaluation of this combination in NSCLC is warranted.

INTRODUCTION
Control of systemic metastases is the single greatest challenge to improving the long-term survival rate of patients with NSCLC. Nearly 70% of patients have locally advanced or metastatic disease at the time of diagnosis. Of those patients who present with completely resectable disease, 50% will eventually develop recurrent disease, the vast majority of which is systemic. Patients with locally advanced NSCLC are usually treated with platinum-based chemotherapy plus radiation therapy and/or surgical resection. Patients with metastatic disease are treated with chemotherapy alone. The prognosis for these patients remains poor as 5-year survival rates range from 5 to 30% for patients with stage III disease. Even with the best available therapies, long-term survival in patients with stage IV disease is unlikely, with 1-year survival rates that are generally in the range of 30% (3). The development of more effective systemic therapy is critical to better control micrometastases in patients with resectable and locally advanced disease and to improve median survivals in patients who present with systemic metastases.

CPT-11 is a water-soluble prodrug that is metabolized in vivo to an active metabolite, SN-38. SN-38 interacts with topoisomerase I, an enzyme that relieves torsional strain in DNA during DNA replication and transcription and stabilizes the DNA cleavage reaction of the enzyme (4–6). During cell division, DNA replication forks collide with these enzyme-DNA cleavage complexes, resulting in double-stranded DNA breaks and subsequent programmed cell death (7, 8).

Because cisplatin represents one of the most active chemotherapeutic agents for NSCLC, the combination of CPT-11 with cisplatin in the therapy of this disease is a logical area of investigation. Therapeutic synergy for these agents has been demonstrated in human lung cancer xenograft models (9, 10). The exact mechanism for the synergy observed between platinum and topoisomerase targeting agents is not well understood; however, simultaneous exposure or sequencing of the platinum compound just prior to the topoisomerase agent appears optimal.
were 30 mg/m\(^2\) cisplatin, followed immediately by 65 mg/m\(^2\) of such a regimen and found it to be quite well tolerated. For PATIENTS AND METHODS open-label, nonrandomized, multicenter, academic- and com-
titration cycle (16). The current trial was undertaken to eval-
ent of the efficacy and safety of this weekly regimen in an

data suggesting a therapeutic advantage to delivering both
agents on the same day and sequencing cisplatin prior to

Given the laboratory

for patients, the recommended starting doses
were 30 mg/m\(^2\) cisplatin, followed immediately by 65 mg/m\(^2\) CPT-11 on a weekly schedule for 4 of 6 weeks for each
treatment cycle (16). The current trial was undertaken to evaluate
the efficacy and safety of this weekly regimen in an

agents on the same day and sequencing cisplatin prior to

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in an open-label, nonrandomized, multicenter, academic- and com-

were enrolled if they met the following criteria: (a) histologically or
cytologically confirmed stage IIIB (with malignant pleural ef-
fusion) or stage IV NSCLC; (b) bidimensionally measurable
disease, at least one area of which had not been subject to prior
irradiation; (c) no prior chemotherapy or immunotherapy; (d) at
least 2 weeks since radiation therapy and full recovery from any
adverse effects; (e) ECOG performance status of 0, 1, or 2; (f)
no evidence of active invasive second malignancy; (g) adequate
organ function as documented by granulocyte count
$\geq 1,500/\mu l$, platelet count $\geq 100,000/\mu l$, hemoglobin $\geq 9 g/dl$, serum creati-
ine $\leq 1.5 g/dl$, total bilirubin $\leq 2.0 g/dl$, and serum glu-
tamic oxaloacetate transaminase $\leq 3$ times the institutional up-

ecological oxaloacetate transaminase $\leq 3$ times the institutional up-

in an open-label, nonrandomized, multicenter, academic- and com-

The pretreatment

were included.

Patients were not eligible for study enrollment if they had
any of the following: (a) active or uncontrolled infection; (b)
significant cardiovascular disease (uncontrolled hypertension,
unstable angina, active congestive heart failure, myocardial in-
farction within the previous 6 months, or uncontrolled serious
arrhythmia); (c) pregnancy, lactation, or refusal to use effective
contraception; (d) any other severe, concurrent illness which in
the judgment of the investigator would make the patient inap-
propriate for entry into this study; (e) Gilbert’s disease was
excluded given recent evidence of excessive CPT-11-induced
neutropenia in patients with this disease; or (f) uncontrolled
diabetes mellitus.

All study candidates were required to provide written in-
formed consent as approved by local institutional review boards
before initiation of any study procedures. Patients were enrolled
both at academic institutions (Vanderbilt-Ingram Cancer Center,
Fox Chase Cancer Center, and West Virginia University Med-
ical Center) and at community hospitals via the Vanderbilt-
Ingram Cancer Center Affiliate Network.

Treatment and Evaluation Plan. The pretreatment
evaluation included medical history and physical examination,
laboratory evaluation (complete blood count, serum chemistries,
and pregnancy test for women of childbearing potential), and
baseline tumor measurement. Medical history, complete blood
counts, and serum creatinine were obtained prior to each chem-
otherapy treatment. Physical examination, performance status,
weight, complete blood counts, liver function tests, and full
serum chemistries were repeated prior to each 6-week cycle.

The weekly cisplatin/CPT-11 regimen used the starting
doses and treatment schedule recommended by Saltz et al. (16)
after their Phase I study of this regimen. Therapy was given in
repeated 6-week cycles comprising weekly treatment with both
drugs for 4 weeks, followed by a 2-week rest. Cisplatin was
given as a 30-min i.v. infusion at a starting dose of 30 mg/m\(^2\);
immediately following the completion of cisplatin administra-
tion, CPT-11 was given as a 30-min i.v. infusion at a starting
dose of 65 mg/m\(^2\).

Patients received standard i.v. hydration with 5% dextrose
in normal saline or normal saline for 2 h to assure adequate
hydration before cisplatin administration. Cholinergic symp-
toms occurring during or within 1 h after receiving CPT-11
could be treated with atropine (1 mg or as needed; Ref. 17).
Dexamethasone (10 mg) was administered as part of the pre-
treatment antiemetic regimen unless a contraindication to corti-

costeroid use was identified. Ondansetron or granisetron (per
physician preference) was given prior to each cisplatin dose.
Loperamide was provided as therapy for delayed diarrhea (18).
Patients were instructed to begin taking loperamide at the first
sign of diarrhea (i.e., first poorly formed or loose stool or first
episode of one to two more bowel movements than usual in 1
day) that occurred $\geq 12$ h after CPT-11 administration. Loper-
amide was to be taken in the following manner: 4 mg at the first
onset of diarrhea, then 2 mg every 2 h around the clock until
diarrhea free for at least 12 h. During the night, patients were
allowed to take 4 mg every 4 h.

All toxicities were graded according to the National Cancer
Institute Common Toxicity Criteria. For subsequent treatment
cycles, the CPT-11 dose was increased to a maximum of 95
mg/m\(^2\) in stepwise increments of 10 mg/m\(^2\) in patients experi-
encing $\leq$ grade 1 hematological and nonhematological toxicity.
CPT-11 was reduced to 55, 45, or 35 mg/m\(^2\) in stepwise de-
crements in patients experiencing $\geq$ grade 2 toxicity. Cisplatin
dose escalation was not permitted. Cisplatin dose was reduced by
50% ($\leq$ 15 mg/m\(^2\)) for serum creatinine of 1.5–2 mg/dl and
omitted for a serum creatinine $>2$ mg/dl.

During a course of treatment, CPT-11 doses were de-
creased by 10 or 20 mg/m\(^2\) for grade 2 or 3 hematological
toxicities or diarrhea, respectively. Cisplatin doses were
decreased by 25% for any grade 2 toxicity, except diarrhea. Grade
3 hematological toxicity required reduction of cisplatin dose by
50%. Cisplatin was not dose adjusted for grade 2 or 3 diarrhea.
Both agents were held for grade 3 nonhematological toxicity,
any grade 4 toxicity, grade 4 diarrhea, or neutropenic fever. A
total of six cycles of treatment were planned. Patients were to be
discontinued from study participation if they withdrew consent,
had disease progression, experienced unacceptable drug toxicity
not responding to dosage modification, or developed an inter-
current, noncancer-related illness that prevented therapy contin-
uation or regular follow-up.

Tumor response was assessed according to WHO criteria
(i.e., measurable disease, evaluable disease, nonevaluable dis-
ease, complete response, partial response, stable disease, and
progressive disease). Tumor reassessment by the same imaging
method used to establish baseline tumor measurement was gen-
Weekly CPT-11 and Cisplatin in NSCLC

**Table 1** Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years, range)</td>
<td>59 (44–79)</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>Females</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Stage at original diagnosis (n, %)</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>IV</td>
<td>43 (86%)</td>
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<tr>
<td>Baseline PS (n, %)</td>
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<tr>
<td>0</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>1</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>2</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Prior treatment (n, %)</td>
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</tr>
<tr>
<td>Surgery</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Surgery and radiation</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>None</td>
<td>31 (62%)</td>
</tr>
</tbody>
</table>

**RESULTS**

**Patient Characteristics.** Between August 1997 and June 1998, a total of 50 patients (30 men and 20 women) were enrolled at multiple institutions (Table 1). The median age was 59 years (range, 44–79 years). Seven patients (14%) had stage IIIB disease, and 43 patients (86%) had stage IV disease. All stage IIIB patients had malignant pleural effusions. Among patients with stage IV disease, 27 patients had one metastatic site, 13 had two sites of involvement, 1 had three sites, and 2 had four different sites involved. Brain, bone, and liver involvement was observed in 10, 22, and 8% of patients, respectively. The majority of patients (56%) had symptoms related to their NSCLC, as evidenced by baseline performance status of 1 or 2. None of the patients had undergone prior chemotherapy. Five patients (10%) had undergone an attempt at primary surgical resection, and 4 (8%) had received prior radiotherapy to tumor sites, whereas 10 (20%) had received both radiation and surgery.

**Treatment Administration.** A total of 160 cycles of chemotherapy were administered. The median number of 6-week cycles/patient was 3 (range, 1–6). Omissions of CPT-11 were infrequent, occurring for only 6.4% (33 of 516) of the planned doses and in 18.6% (30 of 160) of the cycles. The common reasons for omitting CPT-11 were diarrhea (33%), myelosuppression (21%), and intercurrent illness (15%). Seventy % (23 of 33) of the omitted doses were in weeks 3 or 4 of treatment. Eighteen % (93 of 516) of cisplatin doses were held in 33.5% (54 of 160) cycles; 66% (61 of 93) of these dose omissions were in weeks 3 or 4. The common causes for omitting cisplatin were creatinine elevation (35%), vomiting (8%), myelosuppression (14%), and diarrhea (7%).

The mean doses of CPT-11 (expressed as a percentage of dose planned) at the start of cycles 1, 3, and 6 were 100, 96, and 92%. CPT-11 was dose escalated to 75, 85, or 95 mg/m² in 8.8, 1.8, and 1.2% of the 160 total treatment cycles. CPT-11 doses were reduced by one, two, or three levels in 31, 9.9, and 9.2% of cycles, respectively. Myelosuppression (43%; 31 of 72) and diarrhea (48%; 35 of 72) were the major reasons for dose reduction. Mean cisplatin doses (expressed as a percentage of dose planned) at the start of cycles 1, 3, and 6 were 100, 96, and 70%, respectively. Cisplatin dose escalation above the starting dose of 30 mg/m² was not permitted. Cisplatin was reduced to 22.5 mg/m² (25% dose reduction) and to 15 mg/m² (50% dose reduction) in 36 and 8.5% of the 160 total treatment cycles, respectively. Myelosuppression (54%; 35 of 64), vomiting (29%; 19 of 64), and elevated creatinine (11%; 7 of 64) accounted for the dose reductions.

The intended dose intensities for CPT-11 and cisplatin were 43.3 and 20 mg/m²/week, respectively. When considering both dose omissions and modifications, the mean delivered dose intensities for CPT-11 and cisplatin were 38.7 mg/m² (89% relative dose intensity) and 12.7 mg/m² (62% relative dose intensity), respectively.

**Efficacy.** The cutoff date for analysis was December 1999. An intent to treat efficacy analysis was performed, with all 50 patients included. Objective tumor responses were observed in 18 patients (36%; 95% CI, 24–54%). All 18 responses were partial. Stable disease was observed in 39% (19 of 50) of patients. The remaining patients had progressive disease (16%; 8 of 50) or went off study prior to initial tumor reevaluation (10%; 5 of 50).

The median follow-up for patients still alive was 15.6 months (range, 12.5–21.9 months). Median time to response was 3.3 months (range, 1.2–8.9 months), and median duration of response from the time of first evidence of objective response was 4.2 months (range, 0.4–14.1 months). Estimated median time to tumor progression was 6.9 months (range, 0.6–15.2 months; Fig. 1). Median survival was 11.6 months (95% CI, 8.06–15.6), and the 1-year survival rate was 46% (Fig. 2). Objective response, time to disease progression, and median survival for patients with stage IIIB disease (7 patients) were 28%, 10.6 months, and 15.6 months, respectively. For stage IV patients, the results were 37.2%, 6.7 months, and 10.9 months, respectively. The objective response rate, time to tumor progression, and median survival for PS 2 patients (9 patients) were 33%, 3 months, and 3.86 months, respectively. For PS 0, 1

**Statistical Considerations.** A two-staged Simon accrual design was used (19). An overall response rate of 20% was assumed for standard therapy, and a target response rate of 40% was established. Assuming a dropout rate of 10%, a sample size of 50 patients provided at least 83% power and a type 1 error of <5%. If 17 responses occurred in 43 patients, a 95% CI of 25–56% would be achieved. Given that this was a Phase II trial, a sample size of 50 was expected to yield meaningful results with acceptable power. Time-to-event end points were calculated using Kaplan-Meir methods with appropriate censoring.
patients, the results were 36.5%, 7 months ($P = 0.0012$), and 14.7 months ($P = 0.0015$), respectively.

Safety. Clinically important grade 3/4 nonhematological toxicities included expected gastrointestinal events of vomiting (in 12% of patients and 4% of cycles) and late-onset diarrhea (in 26% of patients and 11% of cycles; Table 2). There was one grade 3 and one grade 4 case of cisplatin-induced peripheral neuropathy. Grade 3 or 4 renal toxicity was not observed.

The principal grade 3 or 4 hematological toxicity was neutropenia in 26% of patients and 12% of treatment cycles (Table 2). Three patients (6%) had neutropenic fever, defined as grade 4 neutropenia with simultaneous fever ≥ grade 2. There was one treatment-related death secondary to neutropenic sepsis. Grade 3 or 4 anemia was observed in 14% of patients in 5% of cycles. Twenty-eight patients (56%) received erythropoietin. Three patients required a total of five units of packed red cell transfusions. Grade 4 thrombocytopenia was seen in 14% of patients and 6% of cycles.

DISCUSSION

In Phase III multicenter trials, modern platinum-based chemotherapy regimens effect response rates in the range of 25–41%, median survivals of 8–10 months, and 1-year survival rates of 30–43%, depending to some extent on the population entered (20–29). These trials documented that newer cisplatin regimens containing vinorelbine, gemcitabine, or paclitaxel appear to effect modest improvement in median survival compared with single-agent cisplatin. Although these modest advantages have been long awaited and hopefully will translate into long-term survival advantages when used in the neoadjuvant and adjuvant settings, substantial progress in developing more effective systemic therapy must occur if a significant improvement in 5-year survival rates is to be realized. To this end, identification of new active single agents and combination regimens is critical.

Single-agent CPT-11 is active in patients with advanced NSCLC, and there is evidence for synergy with cisplatin in preclinical models (9–10). Phase I studies of monthly cisplatin with weekly CPT-11 were carried out by Japanese investigators, and therapeutic outcomes were encouraging (12–14, 30). We recently reported the results of the first United States Phase II trial using the monthly cisplatin with weekly CPT-11 regimen in patients with advanced NSCLC (15). Therapeutic outcomes were comparable with those seen with other newer regimens including an objective response rate of 28.8%, median survival of 9.9 months, and 1-year survival rate of 37%. The latter trial was conducted at four academic centers and included patients with ECOG performance status 0–2.

The current trial was undertaken because same-day administration of cisplatin followed by CPT-11 is a potentially more effective method of combining these agents. Furthermore, Phase I trials suggested that tolerability might be superior, in part because of the lower dose and more frequent administration of cisplatin (16). Indeed, typical cisplatin toxicities were less than or equal to those observed in our previous Phase II trial using the monthly cisplatin regimen. Grade III/IV nausea, vomiting, neuropathy, and elevated creatinine were 12% versus 33%; 12% versus 14%; 4% versus 4%; and 0 versus 4% in the weekly versus monthly regimens. Grade III/IV diarrhea was higher with the weekly regimen (26% versus 17.3%, respectively), but dose adjustments largely alleviated this problem in subsequent cycles. As further evidence for the weekly regimen’s tolerability, the median number of treatment cycles was three, and dose intensity was well maintained for both agents. Because treatment cycles with this regimen are of 6 weeks duration, the three cycles of therapy are equivalent to six cycles of a conventional 3-week/cycle regimen. A majority of the dose omissions for both cisplatin and CPT-11 occurred in weeks 3 or 4. In future studies using weekly irinotecan and cisplatin, rather than modifying the doses of CPT-11 and/or cisplatin, it may be more prudent to alter the schedule slightly. For example, changing to a 21-day schedule with weekly drug administration in weeks 1 and 2, followed by a 1-week rest, may help preserve dose intensity.

The current trial was undertaken with patients treated in...
both the academic and community practices settings that included the Vanderbilt-Ingram Cancer Center, Fox Chase Cancer Center, West Virginia University and the Vanderbilt-Ingram Cancer Center Affiliate Network. Two previous Phase II trials carried out in these centers investigated 24-h paclitaxel and 1-h paclitaxel plus carboplatin regimens (31, 32). Respective response rates (21 and 25%), median survivals (8.8 and 7.4 months), and 1-year survival rates (32 and 31%) observed in these two studies were virtually identical when these regimens were subsequently evaluated in multicenter Phase III trials (20, 26). Therefore, relative to our own historical controls, we are encouraged that the weekly cisplatin plus CPT-11 regimen may offer superior efficacy to that of currently used regimens. This can only be addressed in a Phase III trial.

In conclusion, this multicenter academic- and community-based Phase II trial demonstrated superior efficacy for a weekly cisplatin and CPT-11 regimen when contrasted with results observed in historical controls. Tolerability was remarkably good, thus allowing for maintenance of dose intensity and prolonged treatment duration. A Phase III comparison to an approved regimen is currently in development.

REFERENCES


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