Phase I/II Trial of Irinotecan, Carboplatin, and Paclitaxel in Advanced or Metastatic NSCLC

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This multicenter study enrolled 73 patients with locally advanced or metastatic non–small-cell lung cancer (NSCLC). The study design was based on the hypothesis that the non-overlapping toxicities of a 3-drug combination regimen might lead to improved outcomes.

**Introduction**

Following a first report of this combination in 1995,[1] the combination of carboplatin (Paraplatin) administered at an area-under-curve (AUC) dosing and 3-hour infusional paclitaxel (Taxol) rapidly became the favored first-line regimen for the treatment of patients with advanced or metastatic non–small-cell lung cancer (NSCLC). Follow-up reports established its ease of administration, favorable toxicity profile, and more recently, efficacy equivalent to other established first-line combination regimens such as cisplatin (Platinol, CDDP) and vinorelbine (Navelbine).[2-4] The low incidence of severe neutropenia and near absence of severe thrombocytopenia with the carboplatin (Paraplatin) and paclitaxel combination led to the hypothesis that a third active agent could be added to this regimen with the possibility of further therapeutic gains.[5] This hypothesis was supported further by the recent confirmation that the combination of carboplatin and paclitaxel produces significantly less severe toxicity than (1) cisplatin combined with either gemcitabine (Gemzar), docetaxel (Taxotere), or 24-hour infusional paclitaxel in patients with poor performance status NSCLC, or (2) cisplatin combined with vinorelbine in patients with good performance status NSCLC.[4,6]

Irinotecan (Camptosar, CPT-11), a semisynthetic derivative of camptothecin, is a novel topoisomerase-I inhibitor with significant activity in NSCLC patients. Single-agent phase II trials in Japan and the United States that used a weekly schedule of 100 mg/m²/week or an every-3-week schedule of 250 to 350 mg/m² in patients who had not previously received chemotherapy, reported response rates in the range of 11% to 34%. Dose-limiting toxicity in these studies consisted primarily of diarrhea, which occurred 1 to 2 weeks following the start of treatment and was moderate to severe (grade 3 to 4) in 10% to 20% of patients. Severe (grade 4) hematologic toxicity occurred in less than 5% of patients and febrile neutropenia was rare. Three phase II clinical trials investigating irinotecan in combination with cisplatin have reported objective responses in the range of 31% to 54%.[9-11]

Because of its activity in NSCLC as well as its unique mechanism of action and favorable toxicity profile, we hypothesized that irinotecan could be added to near-standard doses of the combination of carboplatin and paclitaxel and that the potential pharmacodynamic interactions of these agents might produce response and survival rates that eventually could be superior to those associated with carboplatin and paclitaxel alone. Therefore, in 1996, we initiated a two-step phase I/II trial of the combination of irinotecan, carboplatin, and paclitaxel. Our primary goal was to determine the maximum tolerated dose (MTD) of irinotecan that could be combined with fixed doses of carboplatin and paclitaxel in patients with stage IIIB or IV NSCLC. The secondary objectives were to determine the toxicity profile of this new combination and to obtain data regarding its efficacy in this disease.

**Methods**

**Patient Eligibility Criteria**

Eligible patients included male or female patients over the age of 18 years with a histologic diagnosis of TNM stage IIIB or IV non–small-cell lung cancer, Southwest Oncology Group (SWOG) performance status of 0 to 2, and a life expectancy equal to or greater than 3 months. Disease could...
be evaluable or objectively measurable for the phase I portion of the study, but had to be objectively measurable for the phase II portion. Adequate hematologic, hepatic, and renal function were required. These were defined by the following laboratory values measured within 7 days prior to study registration: white blood cells (WBC) $\geq 3,500$/mm$^3$, absolute neutrophil count (ANC) $\geq 1,500$/mm$^3$, platelet count $\geq 100,000$/mm$^3$, serum bilirubin $\leq 1.25$ times the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $< 3$ times ULN, and calculated creatinine clearance (Cockroft method) $\geq 50$ mL/minute. Patients with a previous history of brain metastases from NSCLC were eligible if 3 or more weeks had elapsed since completion of radiation therapy, and if they were neurologically improved and stable.

Patients were not eligible for the study if they had a history of seizures, other malignancy within the preceding 5 years (except for adequately treated basal or squamous cell skin cancer and in situ cervical cancer), or prior chemotherapy. Patients with significant cardiovascular disease, serious active infection, uncontrolled diabetes mellitus, peripheral neuropathy, or interstitial lung disease were ineligible. Pregnant or lactating women were excluded, and men or women of reproductive potential were required to use effective contraceptive methods.

**Pretreatment Evaluation**

Within the 21-day period preceding treatment, all patients were required to undergo a complete history and physical examination, screening electrocardiogram, computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain, radionuclide bone scan (if clinically indicated), and objective measurement of measurable disease lesions using appropriate scans or x-rays. Within 7 days of starting treatment, a complete blood cell count with differential and platelet count and complex metabolic panel were required for all patients; female patients had to have a negative pregnancy test.

**Treatment Plan**

The trial was designed to follow a two-step plan. It began with a phase I dose-seeking study with a starting dose of irinotecan at 40 mg/m$^2$ administered intravenously over 90 minutes on days 1 and 8 combined with carboplatin at an AUC of 6 (Calvert method) and paclitaxel 225 mg/m$^2$ infused over 3 hours on day 1 (regimen A, below). This regimen was to be recycled every 3 weeks and the dose of irinotecan was to be escalated (80, 100, 120 mg/m$^2$, etc) in new cohorts of patients until the maximum tolerated dose was achieved. However, as detailed below, unexpectedly severe toxicity was observed at the starting dose level, prompting a change in the treatment plan.

The amended treatment plan called for a starting dose of irinotecan at 40 mg/m$^2$ IV over 90 minutes on day 1 only combined with carboplatin at an AUC of 5 (Calvert method) and paclitaxel 175 mg/m$^2$ infused over 3 hours on day 1 every 3 weeks (regimen B, below). The dose of irinotecan was to be escalated (80, 125, 175 mg/m$^2$, etc) in new cohorts of patients until the maximum tolerated dose was determined.

After the phase I portion of this clinical trial was completed, the phase II portion was conducted at the maximum tolerated dose level in an additional 30 to 40 patients with objectively measurable disease in order to more fully characterize its toxicity profile and to obtain preliminary efficacy data.

**Definitions**

For this study, dose-limiting toxicity (DLT) was defined as first-course grade 4 diarrhea despite aggressive loperamide (Imodium) therapy, any grade 4 thrombocytopenia or neutropenic fever, any grade 3 or 4 nonhematologic toxicity (except nausea, vomiting, or grade 3 diarrhea), or failure to sufficiently recover from toxicities by day 36 of the first course. The maximum tolerated dose was defined as the dose level immediately preceding the dose where $\geq 2$ of 6 patients ($\geq 33\%$) experienced dose-limiting toxicities during the first course. The study plan allowed selection and exploration of an intermediate dose level between two preplanned dose levels. Standard definitions for complete response (CR), partial response (PR), stable disease, and disease progression were used in patients with objectively measurable disease. Survival was calculated from the date of study entry.

**Patient Evaluations**

Adverse events and hematologic toxicities were monitored at weekly intervals or more frequently if clinically indicated. Tumor assessments (in patients with objectively measurable or evaluable disease) were obtained at baseline (prestudy) and after every other course of treatment (every 6 weeks). Complete and partial responses required confirmation 4 to 6 weeks following first documentation.

**Patient Characteristics**

Thirty-three patients were enrolled in the phase I portion of the study (including 6 for regimen A, and 27 for regimen B); 40 additional patients with objectively measurable disease were entered into the
Results

Treatments Administered
Of 33 patients entered into the phase I portion of this study, 32 received a total of 151 courses of treatment (one patient entered did not receive treatment), and the 40 patients entered into the phase II portion of this study received 198 courses of treatment at the time of this analysis (several patients continued to receive treatment after this analysis was performed). The total, median number, and range of treatment courses administered at each dose level is summarized in Table 2.

Toxicity
Among the patients entered into the phase I portion of this study, 33 are evaluable for toxicity, including 6 patients entered at the starting dose level in regimen A, and 26 patients entered at the four dose levels explored in regimen B. Of six patients entered at the irinotecan starting dose level of 40 mg/m² days 1 and 8 (regimen A), three experienced one or more dose-limiting toxicities including one grade 4 diarrhea with febrile/septic neutropenia, two grade 4 neutropenia, and one grade 3 neuropathy. This unexpectedly severe level of toxicity occurred despite the fact that the irinotecan dose on day 8 was withheld in four of the six patients, thus, prompting a change in the treatment plan.

The new treatment plan (regimen B) began with a starting dose of irinotecan 40 mg/m² on day 1 only combined with a decrease in the dose of carboplatin from an AUC of 6 to an AUC of 5 (Calvert method) and a decrease in the dose of paclitaxel from 225 mg/m² to 175 mg/m². At this new starting-dose level, only one of 10 patients experienced first-course dose-limiting toxicities consisting of grade 4 neutropenia, diarrhea, and fever. Escalation of the irinotecan dose to 80 mg/m² did not produce first-course grade 3 to 4 toxicities in five patients. At the 125 mg/m² dose level of irinotecan, however, first-course dose-limiting toxicities occurred in three of eight patients. Since no dose-limiting toxicities had been observed at the preceding 80 mg/m² dose level, a 100 mg/m² dose level of irinotecan was explored in three patients. The absence of first-course dose-limiting toxicities prompted us to further explore this dose level in 40 patients with objectively measurable disease during the phase II portion of the study. Phase I first-course dose-limiting toxicities are summarized in Table 3.

All 40 patients entered into the phase II portion of this study were evaluable for toxicity. All the grade 3/4 hematologic and nonhematologic toxicities observed in 198 treatment courses administered to these 40 patients and the 151 treatment courses administered to the 32 evaluable patients entered into the phase I portion of the study are summarized in Table 4. Grade 4 neutropenia was the most common dose-limiting toxicity, occurring in 14 of 40 patients (35%) in phase II and 13 of 32 patients (41%) in phase I. Neutropenic fever occurred in 12 (30%) patients (10 with grade 4 neutropenia and two with grade 3 neutropenia) in phase II and in four (12.5%) patients (all four with grade 4 neutropenia) in phase I. Grade 3/4 diarrhea was the most common nonhematologic toxicity, occurring in five (12.5%) patients in phase II and in six (18.5%) of the patients in phase I. Grade 3/4 thrombocytopenia, neuropathy, or asthenia each occurred in less than 10% of patients in both phases of the study. At least one episode of grade 3 vomiting occurred sometime during treatment in 6 of 40 (15%) patients in phase II, but in only 1 of 32 (3%) patients in phase I.

Efficacy
An objective response could be assessed in 31 of 33 patients in phase I (one patient was not evaluable and one patient was without objectively measurable disease) and in 33 of 40 patients in phase II (2 patients were not evaluable for response and evaluation was premature for 5 patients). Unconfirmed objective responses occurred in 20 of 31 patients in phase I (a 64.5% overall response rate) including 3 CRs and 17 PRs; 3 CRs and 10 PRs (42%) were confirmed. Unconfirmed objective responses occurred in 20 of 33 patients in phase II (a 60.6% overall response rate) including one CR and 19 PRs; 1 CR and 16 PRs (51%) were confirmed. Table 5 details tumor response according to baseline patient characteristics. The median time to progression and median survival in 32 patients in phase I was 7.1 months and 11.6 months, respectively. The 1-year survival in this group was 46.9%.

Conclusions
The design of this two-step phase I/II trial was based on the hypothesis that the relatively nonoverlapping toxicities of irinotecan and the combination of carboplatin and paclitaxel would allow
us to add nearly full doses of the former to near standard doses of the latter combination. In the phase I portion of this trial, it appeared that the maximum tolerated dose of irinotecan that could be incorporated into this regimen was 100 mg/m², but that this required a reduction in the standard doses of carboplatin and paclitaxel from an AUC of 6 to an AUC of 5 and from 225 mg/m² to 175 mg/m², respectively. However, in the phase II portion of the trial, the toxicity of this new triple combination was unacceptably severe. Of 40 patients with advanced or metastatic non-small-cell lung cancer, 14 suffered grade 3/4 neutropenia (35%) and 30% suffered febrile or septic neutropenia. We are now exploring an additional reduction in the dose of carboplatin to an AUC of 4 in the hopes of reducing the incidence of severe hematologic toxicity to a lower and more acceptable level. Despite the toxicity, the triple combination of irinotecan, carboplatin, and paclitaxel appears to have a high level of activity in NSCLC. Our preliminary data indicate an objective response rate greater than 60% and median survival of approximately 1 year. Although patient selection can often inflate therapeutic outcomes in uncontrolled phase II clinical trials, this usually occurs when trials are conducted at single institutions rather than the multi-institutional setting in which this trial was conducted. Nevertheless, a well-designed, prospectively randomized, clinical trial comparing this triple combination to the double combination of carboplatin and paclitaxel administered at standard doses would be required before any definitive conclusions could be drawn regarding the efficacy of this new regimen and such a trial appears to be warranted. The efficacy and, even more, the toxicity of this triple combination strongly suggests that there are significant pharmacokinetic and/or pharmacodynamic interactions among these agents. It is notable that the doses of irinotecan, carboplatin, and paclitaxel that we are currently exploring represent reductions of 77%, 33%, and 22% from standard doses of these agents on an every-3-week schedule. Any favorable patient selection that would have inflated the response or survival rates would have served to deflate toxicity, but toxicity was clearly and unexpectedly severe. Therefore, these drug interactions appear to be real and, if they occur at the pharmacodynamic level, are extraordinary. Further investigation of the pharmacokinetic and pharmacodynamic interactions of these compounds is needed.

References:


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