Irinotecan Plus Cisplatin in Patients With Advanced Non-Small-Cell Lung Cancer

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During the 1980s, platinum-based regimens were yielding response rates typically less than 25%, median survival durations of about 25 weeks, and 1-year survival rates less than 25% in patients with advanced non-small-cell lung cancer.

Introduction

Preclinical and early phase clinical studies have demonstrated that irinotecan (CPT-11 [Camptosar]) is active against non-small cell lung cancer, [1-8] with single-agent activity similar to that reported for other newer agents introduced during the 1990s, including vinorelbine (Navelbine), gemcitabine (Gemzar), paclitaxel (Taxol), and docetaxel (Taxotere).

During the 1980s, platinum-based regimens for advanced non-small cell lung cancer were yielding response rates typically less than 25%, median survival durations of about 25 weeks, and 1-year survival rates less than 25%. Currently, results from single institution phase II trials of agents introduced during the 1990s are showing a doubling of these numbers, with response rates of 50%, median survival durations of 50 weeks, and 1-year survival of 50%. Multiinstitutional trials are showing response rates ranging from 30% to 40%, median survival durations of 40 weeks, and 1-year survivals of 40%.

This review will provide an overview of data from phase II trials of irinotecan both as a single agent and in combination with cisplatin in Japan and in the United States. The focus will be on preliminary data from the first US trial of irinotecan plus cisplatin in patients with advanced non-small-cell lung cancer.

An Overview of Phase II Data

Japan Multicenter Trial of Single-Agent Irinotecan

In the first large multicenter phase II trial of irinotecan, described by Fukuoka and colleagues,[7] 73 patients with chemotherapy-naïve, advanced non-small-cell lung cancer received single-agent irinotecan (100 mg/m²/wk). An overall response rate of 32% and median survival time of 9.8 months were observed. Grade 3 or 4 toxicities included leukopenia (25%), diarrhea (21%), nausea/vomiting (22%), anemia (15%), alopecia (4%), and pneumonitis (3%). Patients did not routinely receive antiemetics or antidiarrheal medications.

Preliminary results of a US multicenter trial of single-agent irinotecan were reported at the American Society of Clinical Oncology meeting in 1997.[9] Irinotecan (100 mg/m²) produced a response rate of 15% and median survival of 6.2 months in 48 patients with chemotherapy-naïve, advanced non-small-cell lung cancer.

Phase I/II Trial of Irinotecan Plus Cisplatin

Recent biological studies have indicated that topoisomerase I may have a role in the subsequent DNA degradation and cell death that follow DNA damage induced by other sources, including cisplatin (Platinol).[10,11] Furthermore, camptothecin appears to enhance this process by stimulating the DNA-cleaving activity of the enzyme. Preclinical studies in lung cancer models demonstrate therapeutic synergy when topoisomerase I-targeting agents are used in combination with cisplatin.[1,12] Because cisplatin is a staple in the management of non-small-cell lung cancer, it is logical to combine these two agents in clinical trials.

To this end, Masuda and colleagues conducted a phase I/II trial of irinotecan and cisplatin in patients with advanced non-small-cell lung cancer.[8] The recommended phase II doses were 80 mg/m² of cisplatin and 60 mg/m² of irinotecan. Cisplatin dose was fixed at 80 mg/m² and given on day 1 of each 4-week treatment cycle. Irinotecan doses were gradually escalated and given on days 1, 8, and...
15. Dose-limiting toxicities included diarrhea and neutropenia. The response rate was 54%. Survival data were not reported. These same investigators attempted to increase irinotecan doses in this regimen by adding granulocyte colony-stimulating factor (G-CSF [Neupogen]).[4] Irinotecan doses could be safely escalated to 80 mg/m² with growth factor support, but further dose escalation was precluded by dose-limiting diarrhea. The response rate was an encouraging 50%.

US Multicenter Study

The first US trial of irinotecan plus cisplatin in patients with advanced non-small-cell lung cancer described herein employed the phase II regimen recommended by Masuda and colleagues without growth factor.[8] End points included response, survival, quality of life, irinotecan pharmacokinetics/pharmacodynamics, and pharmacoeconomics. A preliminary analysis of toxicity and primary efficacy end points is described.

Patients and Methods

Entry criteria included cytologically or histologically confirmed stage IIIb or IV non-small-cell lung cancer with bidimensionally measurable disease; Southwest Oncology Group (SWOG) performance status of 0 to 2; predicted life expectancy of at least 12 weeks; no prior chemotherapy; pretreatment granulocyte count > 1,500/mL; hemoglobin > 9.0 g/dL; and platelet count > 100,000/mL. Patients had to have adequate liver function (bilirubin \(\leq 2.0\) mg/dL and serum glutamic oxaloacetic transaminase [SGOT] \(\leq 3\) times the upper limit of normal) and adequate renal function (serum creatinine \(\leq 1.5\) mg/dL). Patients with controlled brain metastases were eligible.

Treatment Schedule

Irinotecan (60 mg/m²) was administered as a 90-minute infusion in 500 mL of 5% dextrose in water (D5W) on days 1, 8, and 15 of each 28-day treatment cycle. Two hours following the completion of the irinotecan infusion on day 1 only, cisplatin (80 mg/m²) was given as a 30-minute infusion. Patients received aggressive intravenous hydration and conventional antiemetics prior to cisplatin administration. All patients received 10 mg of dexamethasone prior to chemotherapy unless they had a relative or absolute contraindication to corticosteroids.

Irinotecan dose adjustments are outlined in Table 1. Doses were adjusted differently depending on whether adjustments were made during a given cycle of therapy or on day 1 of a subsequent treatment cycle. Dose adjustments were based on the worst grade of toxicity occurring since the last treatment if adjusted during a treatment cycle, or on the worst toxicities occurring during the entire previous cycle of therapy if adjusted on day 1 of a subsequent cycle.

Cisplatin doses were fixed, and dose adjustment was not allowed. Patients who developed prohibitive cisplatin toxicities or a serum creatinine \(\geq 1.5\) g/dL were removed from the study. Loperamide was used for diarrhea in the following manner: All patients were instructed to begin taking loperamide at the earliest sign of diarrhea and/or abdominal cramping that occurred more than 8 hours after receiving irinotecan. They were told to take 4 mg of loperamide orally at the first onset of diarrhea and then 2 mg every 2 hours (except at night during sleep) until they were free of diarrhea for at least 12 hours. During sleeping hours, patients were instructed to take 4 mg of loperamide every 4 hours. Treatment was continued until the development of regimen intolerance or progressive disease.

Treatment Evaluation

Measurable disease was evaluated prior to each treatment cycle. Conventional definitions of partial and complete response and of stable and progressive disease were used. Classification of a partial or complete response required confirmation after at least 4 weeks. Toxicity was graded weekly using the National Cancer Institute (NCI) Common Toxicity Scale. Quality of life was evaluated prior to each treatment cycle using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire.[13]

Plasma for irinotecan pharmacokinetics was sampled prior to treatment and 1, 2, 4, and 24 hours following the completion of the irinotecan infusion during weeks 1 and 3 of the first treatment cycle. Data relating to medical resource utilization were collected weekly and were categorized as related to chemotherapy, hospitalization, outpatient visits, or home care.

Preliminary results of toxicity, response, and survival analyses are reported here. A more detailed report is planned once the final analysis is complete.

Patient characteristics are summarized in Table 2. A total of 52 patients were enrolled, all of whom were evaluable for response, survival, and toxicity. A majority (79%) of patients had stage IV disease, and 85% of patients had a SWOG performance status of 0 or 1. Median age was 61 years.
Toxicity
A total of 217 courses of therapy were given. Grade 3 or 4 neutropenia was the predominant hematologic toxicity, occurring in 46% of patients and 23% of treatment cycles (Table 3). Neutropenia and fever (grade 2 or higher) developed in 6% of patients, but documented serious infection was not observed. Grade 3 or 4 thrombocytopenia and anemia were infrequent, occurring in 12% and 8% of patients, respectively.

Late diarrhea (defined as that occurring >12 hours following treatment) of any grade occurred in 77% of patients and 43% of treatment cycles (Table 4). Grade 3 and 4 late diarrhea occurred in 17% of patients and 6% of treatment cycles.

With the exception of diarrhea, nonhematologic toxicities were typical of more conventional cisplatin-based two-drug combinations used for advanced non-small-cell lung cancer. Other common grade 3 or 4 nonhematologic toxicities included asthenia (23% of patients) and nausea (33%). There were no treatment-related deaths.

Dose Reductions for Toxicity
The median number of treatment cycles was 4 (range, 1 to 14). Most patients (73%) required irinotecan dose reductions. Cisplatin doses were fixed and were not reduced for any toxicity. The most common reasons for irinotecan dose reduction were nausea and vomiting (27% of patients), followed by diarrhea (21%), and neutropenia (12%).

Response and Survival
All patients were evaluated for response and survival. The overall response rate was 28.8% (95% confidence interval [CI], 16.5% to 41.2%). There were two complete responses (4%) and 13 partial responses (25%). Over half (54%) of patients had stable disease, and 17% had progressive disease. There was no correlation of response with age, gender, performance status, or number of metastatic sites.

Median time to progression was 5.1 months (range, 0.7 to 14.1 months); median response duration was 5.9 months (range, 1.0 to 10.6 months); and median survival was 9.9 months (range, 1.0 to 30.8 months). The 1-year survival rate was 37%.

Discussion
Irinotecan demonstrates single-agent activity against advanced non-small-cell lung cancer similar to that reported for other newer active agents, including paclitaxel, docetaxel, gemcitabine, and vinorelbine.[14-16] Preclinical synergy between irinotecan and cisplatin has been observed, and phase I-II trials of this combination in patients with advanced non-small-cell lung cancer have yielded promising results.[1,4,8]

The current trial utilized the Masuda regimen of weekly irinotecan plus monthly cisplatin without G-CSF.[8] Toxicities were typical of those seen with conventional cisplatin-based doublets, although grade 3 and 4 late diarrhea was more frequent. The median survival time of almost 10 months is comparable to that observed with regimens containing other newer active agents in combination with platinum compounds.[14-16] The results of the current trial are especially promising because they were generated by a multicenter trial with relatively relaxed entry criteria, including patients with a performance status of 2 and those with brain metastases.

Possible Flaws of the Study Regimen
Certain components of the study design may have negatively affected therapeutic outcomes, and it is possible that the regimen can be improved. First, cisplatin doses were fixed, and dose reduction for typical cisplatin toxicities was not allowed. Patients experiencing prohibitive cisplatin toxicities or a rise in serum creatinine ≥ 1.5 mg/dL were removed from the study. Furthermore, the predominant toxicity necessitating irinotecan dose reduction was nausea and vomiting, a toxicity more likely related to cisplatin. Most patients had irinotecan dose reductions, resulting in doses (40 mg/m^2) approximately one-third of conventional single-agent doses.

Preclinical trials of topoisomerase-targeting agents indicate that the therapeutic synergy with other DNA-damaging agents requires the presence of both drugs or at least the presence of DNA lesions from both drugs in the cancer cells at the same time.[1,10-12,17-19] In general, it appears that giving the topoisomerase drug second is preferable. Although the mechanism is not yet well characterized, the topoisomerases appear to recognize and bind to DNA damaged by other agents or irradiation, and this action is enhanced in the presence of camptothecin or etoposide. Therefore, optimal sequencing may involve either simultaneous administration or administration of the platinum compound first and the topo-isomerase agent second.

In summary, the current regimen may have failed to optimally exploit the potential therapeutic
synergy between these two agents for the following reasons:

1. Two of three irinotecan doses per cycle were given 1 to 2 weeks after the cisplatin dose and at doses likely to be subtherapeutic.

2. Day 1 sequencing of irinotecan and cisplatin may have been the converse of ideal.

3. Irinotecan doses were unnecessarily attenuated.

**Trials of a More Optimal Regimen**

In an effort to design a more optimal irinotecan/cisplatin regimen that addresses the potential flaws of the current regimen, Saltz and colleagues at Memorial Sloan-Kettering Cancer Center performed a phase I trial of cisplatin plus irinotecan in which both agents were given weekly for 4 to 6 weeks.[20] Cisplatin was administered prior to irinotecan each week. Recommended phase II doses for chemotherapy-naïve patients were 30 mg/m² of cisplatin and 65 mg/m² of irinotecan. At Vanderbilt, we are currently conducting a trial of this regimen in chemotherapy-naïve patients with advanced non-small-cell lung cancer (Table 5). To date, 20 patients have enrolled in this trial. Early results are encouraging from both the therapeutic and toxicity standpoints.

**References:**


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