The Emerging World Role of Irinotecan in Lung Cancer

Irinotecan (CPT-11, Camptosar), either alone or in combination with cisplatin (Platinol), has demonstrated activity in advanced non-small-cell lung cancer (NSCLC). In single-agent studies, response rates as high as 35% have been reported.

Introduction

Lung cancer, with more than 1 million cases diagnosed worldwide annually, has become the most common malignancy in terms of incidence. Although the incidence is starting to plateau in North American men, it continues to rise in North American women and in both genders outside of the United States, particularly in Europe and the Orient. The 5-year survival rate in the United States is 14%, compared with 8% in Europe.[1] Generally, the disease is either systemic at diagnosis, or manifests distant spread after locoregional therapy. Hence, new agents with improved systemic activity are desperately needed.

This article will review the activity of irinotecan (CPT-11, Camptosar), either alone or in combination with cisplatin (Platinol) and other agents, and will address its emerging role as a component of radiosensitizing therapy in locally advanced non-small-cell lung cancer. Planned and ongoing phase III trials to establish the utility of irinotecan in non-small-cell lung cancer and small-cell lung cancer will also be discussed.

Irinotecan Alone and in Combination Therapy

Single-Agent Therapy

Multiple phase II studies, particularly in Japan, have established the utility of irinotecan in the treatment of advanced non-small-cell lung cancer. Response rates have ranged as high as 30% to 35%, using conventional schedules of 100 to 125 mg/m^2 × 4 every 6 weeks,[2-4] or doses of 300 to 350 mg/m^2 every 3 weeks with or without hematopoietic growth factor support.[5] Toxicities have generally included myelosuppression and diarrhea. Work by Kameyama and colleagues on the activation and detoxification of irinotecan by human lung cancer cell lines has revealed expression of the enzyme(s) that convert(s) irinotecan to the active moiety, SN-38 (7-ethyl-10-hydroxycamptothecin).[6] Of 25 squamous cell carcinoma cell lines, 15 (60%) were strongly positive for carboxylesterase, the putative enzyme; of 25 adenocarcinomas, 20 (80%) proved positive, including 4 that were strongly positive.

Irinotecan/Cisplatin Combinations

Cisplatin remains the cornerstone of combination therapy in advanced non-small-cell lung cancer. Consequently, investigators have sought to assess the activity of irinotecan in combination with cisplatin. The earliest efforts in this regard were in Japan. Masuda and colleagues evaluated cisplatin at 80 mg/m^2/d on day 1 every 4 weeks in combination with irinotecan at 60 mg/m^2/d on days 1, 8, and 15.[7] Overall response rate was 52%, time to disease progression was 4.4 months, median survival time was 10.2 months, and the 1-year survival rate was 33%. Ueoka assessed irinotecan and cisplatin in combination at doses of 50 and 60 mg/m^2, respectively, days 1 and 8 every 4 weeks.[8] Overall response rate was slightly lower at 41%, but median survival time was 13 months, and the 1-year survival rate was 58%.

Mori and colleagues conducted a phase II study of bolus irinotecan at 160 mg/m^2 day 1 in combination with cisplatin 20 mg/m^2/d × 4 by continuous infusion with granulocyte colony-stimulating factor (G-CSF [Neupogen]) support.[9] Twenty-four treatment-naive non-small-cell
lung cancer patients with advanced disease were evaluated. Overall response rate was 58.5%, median survival time was 44.8 weeks, and the 1-year survival rate was 44%. Major toxic effects included grade 3/4 diarrhea in 23%, granulocytopenia in 20%, thrombocytopenia in 15%, and anemia in 15% of patients. There were no treatment-related deaths.

In Europe, Cardenal conducted a multi-institutional phase II trial combining irinotecan at 200 mg/m² as a 1-hour infusion in combination with cisplatin at 80 mg/m² every 21 days.[10] Over an 8-month period, 48 patients were recruited with 43 evaluable for toxicity. Grade 4 neutropenia occurred in 11.6%, grade 4 diarrhea in 9.3%, and grade 3 nausea and vomiting in 16.2% of patients. Of 32 evaluable patients, 12 (37.5%) achieved a partial response.

Phase III Randomized Trials

In a phase III trial, Masuda et al assessed irinotecan as a single agent or in combination with cisplatin vs vindesine/cisplatin.[11] Eligible patients had untreated stage IIIB or IV measurable non-small-cell lung cancer, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate marrow, hepatic, renal, and pulmonary function. Patients over 75 years old were excluded. A total of 398 patients were enrolled, of whom 246 had stage IV disease. Demographics with respect to age, performance status, previous weight loss, and levels of albumin and lactate dehydrogenase were well matched for each arm. Patients received one of three regimens: (1) irinotecan 100 mg/m²/d on days 1, 8, and 15 every 4 weeks; (2) irinotecan 60 mg/m²/d on days 1, 8, and 15, and cisplatin 80 mg/m²/d on day 1 every 4 weeks; or (3) vindesine 3 mg/m²/d on days 1, 8, and 15, and cisplatin 80 mg/m²/d on day 1 every 4 weeks.

Trial results are shown in Table 1. Leukopenia was more pronounced with the vindesine/cisplatin combination, while thrombocytopenia was more common in the irinotecan/cisplatin arm. Patients in both irinotecan arms had substantially more grade 3/4 diarrhea compared with those receiving vindesine/cisplatin. The cisplatin arms yielded considerably more grade 3/4 neutropenia and anemia. The incidence of anemia was driven by cisplatin: 39% grade ≥ 3 for irinotecan/cisplatin compared with 23% for vindesine/cisplatin and 6% for irinotecan alone. Among stage IV patients, survival was significantly better in those receiving irinotecan than in those receiving vindesine/cisplatin (Figure 1).

In contrast, results from another phase III trial comparing the two platinum combinations alone did not reveal a significant advantage or disadvantage for irinotecan.[12,13] Again, baseline demographics were well matched for the 117 randomized patients with stage IV disease. Grade ≥ 3 neutropenia was more common in the vindesine/cisplatin arm (83%) than in the irinotecan/cisplatin arm (64%). Grade ≥ 3 anemia was slightly more common with the irinotecan combination: 24% vs 17%. Likewise, grade ≥ 3 nausea/vomiting and diarrhea were more common at 19% and 15%, respectively, for irinotecan/cisplatin vs 12% and 2% for vindesine/cisplatin. Median survival for patients receiving irinotecan/cisplatin was 44.7 weeks, and 1- and 2-year survival rates were 36.4% and 8.7%, respectively, in stage IV patients. Median survival time for vindesine/cisplatin patients was 45.3 weeks, with 1- and 2-year survival rates of 41.4% and 10.3%, respectively (P = .668) (Figure 2). Significant negative prognostic factors included male gender (P = .0028) and performance status of 2 (vs 0/1) (P = .0003).

North American Trials

The initial effort in North America to assess irinotecan combinations, reported by DeVore and colleagues, was similar to the Japanese study of Masuda and colleagues: cisplatin at 80 mg/m²/d on day 1 plus irinotecan at 60 mg/m²/wk × 3 every 4 weeks.[14] Fifty-two patients were enrolled. Overall response rate was 29%, with a median time to progression of 5.1 months, median survival time of 9.9 months, and a 1-year survival rate of 37%. Grade ≥ 3 neutropenia occurred in 46% of patients, with an 11.5% overall incidence of febrile neutropenia. Nausea, vomiting and asthenia were driven by cisplatin: grade ≥ 3 incidences were 32.7%, 13.5%, and 23.1%, respectively. Grade 3/4 diarrhea occurred in 17.3% of patients. The relative dose intensity of irinotecan was 75.5%. Dose reductions of irinotecan were required in 73% of patients; most patients ultimately had the irinotecan dose reduced to ≤ 40 mg/m².
A subsequent follow-up study assessed weekly irinotecan combined with weekly cisplatin.[15] The rationale for this study included the following: (1) the putative synergy of these two agents seen in vitro could be better exploited by same-day administration; (2) improved sequencing of irinotecan and cisplatin might potentially improve efficacy; (3) potentially diminished toxicity could result from decreased cisplatin dose per administration. The regimen was modeled after phase I data of Saltz and colleagues.[16] Eligible patients received irinotecan at 65 mg/m$^2$/wk $\times$ 4, in combination with cisplatin at 30 mg/m$^2$/wk $\times$ 4. Treatment was repeated at 6-week intervals. Fifty patients were enrolled.

Overall response rate (36%) was slightly higher than that in the previous study, median time to progression was 6.9 months, median survival time was 11.6 months, and the 1-year survival rate was 46%. These were the best results observed to date in the Vanderbilt Cancer Center Affiliate Network (VCCAN) trials. Overall incidence of grade $\geq$ 3 neutropenia was 26%; febrile neutropenia occurred in 6% of patients. Grade $\geq$ 3 thrombocytopenia occurred in 14% and grade $\geq$ 3 vomiting in 12% of patients. The relative dose intensity of irinotecan in this combination was 89%, and the dose intensity was fairly well maintained for both agents. Comparison of these two regimens is shown in Table 2. Data to date thus favor using weekly rather than monthly cisplatin.

**Irinotecan/Taxane Combinations**

Burtness and colleagues conducted a phase I trial of irinotecan and paclitaxel (Taxol), both administered weekly $\times$ 4 every 6 weeks.[17] A total of 21 patients received 53 treatment cycles. The maximum tolerated dose at this weekly schedule was 50 mg/m$^2$ of irinotecan and 75 mg/m$^2$ of paclitaxel. Pharmacokinetic evaluations revealed no drug-drug interactions based on irinotecan and SN-38 levels. In an ongoing phase II trial conducted by these investigators, advanced non-small-cell lung cancer patients with performance status 0 to 2 are receiving an abbreviated schedule of this regimen: irinotecan at 50 mg/m$^2$/wk $\times$ 2 every 3 weeks combined with paclitaxel at 75 mg/m$^2$/wk $\times$ 2 every 3 weeks. To date, seven patients have been accrued, and no grade 4 neutropenia has yet been observed (personal communication, J. Murren, 2001). Two of six evaluable patients have a sustained partial response (18+ weeks); three have stable disease and one has had progressive disease. Rosen et al combined irinotecan with paclitaxel, both given once every 3 weeks.[18] The maximum tolerated doses for each agent were 225 and 100 mg/m$^2$, respectively. Grade $\geq$ 3 diarrhea was observed in only one of nine treatment courses at the maximum tolerated doses, whereas at higher doses, grade $\geq$ 3 diarrhea occurred in 5 of 17 patients. Objective responses were seen in non-small-cell lung cancer and occult primary squamous malignancy. Paclitaxel coadministration did not alter irinotecan pharmacokinetics (irinotecan and SN-38 levels).

Sandler and colleagues are conducting phase I and II studies of paclitaxel, irinotecan, and carboplatin (Paraplatin).[19] The maximum tolerated doses for these agents using an every-3-week schedule were paclitaxel at 175 mg/m$^2$, irinotecan at 100 mg/m$^2$, and carboplatin at an area under the concentration-time curve (AUC) of 5. Thirty-two patients were enrolled in the phase I effort; the overall response rate was 40% (10% complete response rate). Median time to progression was 6.8 months, median survival time was 11 months, and the 1-year survival rate was 47%. To date, 40 patients have been enrolled in the phase II effort; the 30% response rate is comparable to that seen in the phase I portion of the trial, time to progression at 5.6 months is similar. The 1-year survival rate is promising at 50%. Disappointingly, the incidence of neutropenic fever is 30%.

Finally, a phase I study assessed irinotecan combined with docetaxel (Taxotere).[20] Twenty-six treatment-naive non-small-cell lung cancer patients with advanced disease (22 with stage IV disease) received docetaxel on day 2 and irinotecan on days 1, 8, and 15. Doses were escalated across sequential cohorts. Maximum tolerated dose for each agent was 50 mg/m$^2$. Higher doses led to dose-limiting toxicity, primarily neutropenia. Overall response rate was 32%, median survival time was 39 weeks, and the 1-year survival rate was 38%.

**Future Efforts in Advanced Disease**

Rocha-Lima has reported the results of a phase I assessment of irinotecan in combination with gemcitabine (Gemzar); each agent can be administered at full dose (irinotecan 100 mg/m$^2$,
gemcitabine 1,000 mg/m²) weekly × 3 every 4 weeks without the need for G-CSF support.[21] The Cancer and Leukemia Group B (CALGB) is spearheading a phase II trial of irinotecan and gemcitabine in advanced non-small-cell lung cancer, and a similar trial as salvage therapy in progressive small-cell lung cancer. A phase III trial comparing cisplatin/irinotecan using a day-1, day-8 schedule every 3 weeks to irinotecan/gemcitabine and gemcitabine/cisplatin is planned. In addition, a phase III study comparing the weekly cisplatin and irinotecan × 4 every 6 weeks schedule to standard therapy is being considered. Finally, in Japan, a four-arm phase III trial comparing the new Japanese standard combination of irinotecan/cisplatin with other state-of-the-art combinations[11]including vinorelbine (Navelbine)/cisplatin, gemcitabine/cisplatin, and carboplatin/paclitaxel[11]s ongoing.

In summary, a survival advantage for stage IV non-small-cell lung cancer patients was observed in at least one trial using monthly cisplatin and weekly irinotecan as compared with vindesine/cisplatin. On the other hand, weekly irinotecan and cisplatin appears to be more active and better tolerated than the monthly schedule. Future studies will elucidate the status of irinotecan combinations vis-à-vis other standard combinations, and will also assess the role of irinotecan, either alone or in combination with gemcitabine, as salvage therapy in previously treated patients.

**Concurrent Irinotecan and Radiation Therapy**

**Locally Advanced NSCLC**

Both irinotecan and cisplatin individually have shown synergistic activity with radiation. Takeda et al.[22] conducted a phase I study of weekly irinotecan combined with standard thoracic radiotherapy (60 Gy) for locally advanced non-small-cell lung cancer. The irinotecan dose was escalated across sequential cohorts starting at 30 mg/m² and increasing by 15 mg/m² per cohort to a maximum of 75 mg/m². A total of 26 patients (20 men and 6 women) were accrued. The median age was 63.5 years; 22 of 26 had a performance status of 0 to 1. All but one had stage IIIB disease; 16 had squamous cell histology. Dose-limiting toxicity was observed at 60 mg/m²: three of five patients experienced grade 3 or 4 esophagitis or pulmonary toxicity. The maximum tolerated dose (recommended dose) was 45 mg/m²/wk. The overall response rate was 76.9%, the 1-year survival rate was 61.5%, and median survival time was 15.7 months.

Fukuda and colleagues combined split-course radiotherapy with two cycles of cisplatin at 60 to 80 mg/m²/d on day 1, and irinotecan at 40 to 60 mg/m²/d on days 1, 8, and 15.[23] The maximum tolerated doses, respectively, were 80 and 60 mg/m². Radiation was given to a total dose of 24 Gy starting on day 2 of cycle 1; 26 to 36 Gy were administered during cycle 2. Twenty-three patients were accrued; four experienced grade ≥ 2 esophagitis. The overall response rate was 65%, and median survival time was approximately 1 year.

Another trial combined standard thoracic radiotherapy, carboplatin, and irinotecan.[24] Thirty-one patients were accrued (24 male); all but two had performance status of 0 to 1. The median age was 62 years. Of 30 evaluable patients, 18 had stage III disease and 19 had squamous cell histology. Patients received carboplatin at 20 mg/m² daily, and sequential cohorts received escalating doses of irinotecan weekly. Again, irinotecan at a dose of 60 mg/m² resulted in unacceptable toxicity: three of three patients at this dose experienced grade 4 pneumonitis. The overall response rate was 60%, median survival time was 15.1 months, and the 1-year survival rate was 56.7%.

Yamamoto conducted a combination trial using induction therapy with irinotecan and cisplatin followed by concurrent chemoradiation with irinotecan alone.[25] Patients received two cycles of full-dose induction treatment: cisplatin at 80 mg/m² days 1 and 29, and irinotecan at 60 mg/m²/d on days 1, 8, 15, 29, 36, and 43. Thoracic radiotherapy followed on day 57; 60 Gy were given over 6 consecutive weeks, combined with irinotecan at 30 mg/m²/wk × 6. A total of 68 patients were enrolled (52 men and 16 women); the median age was 63 years. Approximately two-thirds of the patients had a performance status of 1, 40 had stage IIIB disease, 28 had squamous cell histology, and 27 had adenocarcinoma histology.

The grade 3/4 toxicities that occurred during induction chemotherapy were predictable: neutropenia in 72% of patients and diarrhea in 19%. Grade 3/4 toxicities during concomitant thoracic
radiotherapy/irinotecan consisted of neutropenia in 16% of patients, esophagitis in 4%, and hypoxemia in 6%. There were no treatment-related deaths. The overall response rate was 63.3%, median survival time was quite promising at 19.3 months, and the 1-year survival rate was 65.8%.

North American Efforts

Combined Chemoradiation With Irinotecan

Based on the data generated in Japan,[22-25] and the observation that weekly therapy could potentially enhance radiosensitization while limiting toxicity,[14] Langer et al have initiated a phase I trial in which full-dose radiotherapy (63 Gy) is combined with weekly irinotecan and cisplatin.[26] Eligibility requires measurable non-small-cell lung cancer[7] either locally advanced and surgically unresectable, medically inoperable stage II/IIIA, or locally recurrent after previous surgery. Other entry criteria include Karnofsky performance status $\geq 50$, $\leq 10\%$ weight loss, adequate physiologic indices (absolute neutrophil count $\geq 2,000/mL$, platelet count $\geq 100,000/mL$, creatinine level $\leq 1.5$ mg/dL, bilirubin level $\leq 1.5$ mg/dL), and adequate pulmonary function (FEV1 $\geq 1$ L).

The starting doses for irinotecan and cisplatin were 30 and 25 mg/m$^2$, respectively; seven patients were accrued at this dose level. The first enrollee developed *Aspergillus* pneumonia in the setting of neutropenic fever. The other six have not experienced dose-limiting toxicity. Accrual to dose level 2 (irinotecan at 40 mg/m$^2$ weekly, cisplatin at 25 mg/m$^2$) continues. Grade 3 fatigue and grade 2 diarrhea have been observed in one patient each. Investigators have yet to observe grade 3 esophagitis. Seven of nine evaluable patients have responded.

In a phase I study, Chakravarthy and colleagues studied irinotecan alone, then in combination with carboplatin weekly (at an AUC of 2) plus radical thoracic radiotherapy in 27 patients.[27] The maximum tolerated dose for single-agent irinotecan was 40 mg/m$^2$; it was 30 mg/m$^2$/wk for irinotecan in combination with carboplatin.

Small-Cell Lung Cancer

Results of phase II studies have demonstrated promise for irinotecan as a single agent[28-31] and in combination with cisplatin, in the treatment of advanced small-cell lung cancer. Kudoh et al reported an overall response rate of 86% for this combination.[32] The complete response rate was 29%, median survival time was 13.2 months, and the 2-year survival was 17%. Based on these observations, Noda and colleagues conducted a phase III study comparing a standard regimen of EP (cisplatin [Platinol] at 80 mg/m$^2$ on day 1 and etoposide at 100 mg/m$^2$ on days 1 to 3), every 3 weeks to CP (cisplatin [Platinol] at 60 mg/m$^2$ on day 1 every 4 weeks and irinotecan [Camptosar] at 60 mg/m$^2$ on days 1, 8, and 15) every 4 weeks.[33] Stratification included performance status and institution. Patients whose tumors progressed were taken off study. Those with partial response were observed; and those with complete or near complete response were randomized a second time to either observation or radical thoracic radiotherapy (50 Gy, ie, 2 Gy/d × 5 weeks).

To be eligible, patients had to have cytologically or histologically proven small-cell lung cancer; extensive disease; no previous radiotherapy, chemotherapy, or surgery; ECOG performance status of 0 to 2; age $\leq 70$ years; and adequate physiologic indices (normal marrow, liver, and kidney function). Both treatment arms were well matched with respect to demographics. The median age was 63 years (range: 30 to 70 years). Of 77 patients accrued to each arm, 71 out of 77 in the CP arm and 67 out of 77 in the EP arm had metastatic involvement. Six CP patients and 10 EP patients had a performance status of 2.

The original accrual target for this study was 230 patients; however, enrollment was suspended in December 1998 with 154 patients accrued because of a statistically significant survival difference. In the first analysis, median survival for patients receiving CP was 14 months vs 10 months for those receiving EP. An updated analysis revealed a median survival of 390 days for the CP arm vs 287 days for the EP arm, with 1- and 2-year survival rates, respectively, of 58.4% and 18.9% for CP and 37.7% and 6.5% for EP ($P = .0021$). The overall response rates were 83% and 68% in the CP and EP arms, respectively ($P = .013$). The EP regimen yielded a considerably higher incidence of grade $\geq 3$
neutropenia (92% vs 66%, $P = .0002$) and grade $\geq 3$ thrombocytopenia (18% vs 5%, $P = .01$). Not surprisingly, the CP arm caused substantially more grade $\geq 3$ diarrhea (16% vs 0%, $P = .0001$).

As of this writing, the irinotecan/cisplatin combination has become the standard for future comparison studies in extensive disease in Japan. Two separate North American trials are planned. One will attempt to duplicate the Japanese effort; the other will use a more standard 3-week schedule, ie, etoposide at 100 mg/m$^2$/d $\times$ 3 and cisplatin at 80 mg/m$^2$ on day 1 vs irinotecan at 65 mg/m$^2$ on days 1 and 8 and cisplatin at 30 mg/m$^2$ on days 1 and 8 every 3 weeks. If either North American trial confirms the results of the Japanese study, then the irinotecan/cisplatin combination will likely become a standard treatment worldwide.

**Conclusions**

Irinotecan is a promising agent in the treatment of advanced non-small-cell lung cancer and small-cell lung cancer. Results of ongoing trials will confirm or refute the survival advantage observed for irinotecan in combination with cisplatin in extensive-stage small-cell lung cancer. One of two trials conducted in Japan has already demonstrated a significant survival advantage for irinotecan/cisplatin compared with standard treatment in patients with advanced non-small-cell lung cancer. To date, however, phase III trials focusing on the role of irinotecan in non-small-cell lung cancer have not yet been conducted in North America. Over the next few years, considerably more data on irinotecan will become available regarding its optimal role in the treatment of lung cancer, and comparing it directly with other modern agents, including paclitaxel, gemcitabine, and vinorelbine.

**References:**


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