Irinotecan and Cisplatin in Upper Gastrointestinal Malignancies

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Irinotecan (Camptosar), an active agent in the treatment of fluorouracil-refractory colorectal cancer, has antitumor activity in upper gastrointestinal cancers. Clinical trials from Japan indicate antitumor responses in gastric and

**Introduction**

Camptothecin is a plant alkaloid derived from the *Camptotheca acuminata* tree. The camptothecins act primarily by inhibition of the topoisomerase I enzyme.[1-4] Once bound to the topoisomerase I-DNA complex, the camptothecins block reannealing of the parent DNA, thereby halting nucleic acid synthesis in the cell, leading to cell death.[2-4] Camptothecin sodium was originally evaluated and found active in the late 1960s but demonstrated intolerable toxicities, including diarrhea, myelosuppression, and hemorrhagic cystitis.[5,6]

More recently, irinotecan (Camptosar), a semisynthetic, water-soluble derivative of camptothecin, was found to have more tolerable and predictable toxicity, as well as heightened in vitro and in vivo antitumor activity. Myelosuppression (mainly neutropenia) and diarrhea continue to be dose-limiting toxicities; yet in US studies, grade 3 or 4 leukopenia or severe diarrhea occur in only one quarter of patients. Nausea, vomiting, anorexia, abdominal pain, alopecia, fatigue, fever, pneumonitis, and hemorrhage may be seen. Elevation of serum creatinine, amylase, and liver function values have also been observed.

Irinotecan (CPT-11) is converted by carboxylesterases to its more active metabolite, SN-38, in the liver. In vitro, SN-38 is 250- to 1,000-fold more active an inhibitor of topoisomerase I activity than is irinotecan.[7] The mean terminal half-life of SN-38 in plasma is slightly longer than that of irinotecan (11.5 ± 3.8 vs 6.3 ± 2.2 hours). The time to peak concentration of SN-38 is highly interpatient-dependent, occurring 30 to 90 minutes after the end of the infusion.[8] Murine studies suggest that the liver may concentrate irinotecan, convert it to SN-38, and eliminate both compounds, as well as the glucuronide conjugate of SN-38, via biliary excretion. Renal clearance has not been reported to be a major route of elimination for these compounds in humans.

Several phase I and II studies conducted in Japan, France, and the United States have demonstrated antitumor activity of irinotecan in several tumor types. Irinotecan has been approved for clinical use in Japan for small-cell lung cancer, non-small-cell lung cancer, and uterine and cervical cancers. In the United States, irinotecan is approved for the treatment of fluorouracil (5-FU)-refractory colon cancer.

**Preclinical Studies of Irinotecan**

**Gastric Cancer**

Kawato et al demonstrated the antitumor activity of irinotecan and SN-38 in human gastric adenocarcinoma SC-6 and St-15 xenografts.[9] In these cell lines, irinotecan and SN-38 produced superior responses compared with responses produced by doxorubicin and 5-FU. More recently, Mitsui et al confirmed the activity of irinotecan and SN-38, while demonstrating the superiority of DX-8951f, another camptothecin derivative, against four human gastric cancer cell lines.[10] Antitumor activity of irinotecan (and DX-8951f) was again noted in human gastric adenocarcinoma SC-6 xenografts.

**Esophageal Cancer**
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Irinotecan remains an investigational drug in esophageal cancer. As yet, no formal phase I or II studies have been reported, however, some preclinical data suggest significant activity. Ikeda et al examined the antitumor activity of four camptothecin analogs--DX-8951f, SN-38, 9-aminocamptothecin, and topotecan (Hycamtin)--against six human esophageal cancer cell lines.[11] The authors noted significant antitumor activity of all four analogs, especially DX-8951f. In addition, the cell lines all expressed high levels of topoisomerase I, the target of these camptothecin compounds.

Combination of Irinotecan and Cisplatin

Cisplatin (Platinol) is an alkylating agent that exerts its antineoplastic activity by forming platinum-DNA adducts, leading to impaired DNA synthesis and, ultimately, cell demise. Resistance to cisplatin-based therapy is mediated by rapid repair of these platinum-DNA adducts. This repair requires unscheduled DNA synthesis, which, in turn, requires uncoiling of the damaged section of DNA. The latter process is facilitated primarily by topoisomerase II. Irinotecan, however, appears to prevent the removal of cisplatin-induced adducts, perhaps by the formation of irreversible topoisomerase I cleavage complexes which promote illegitimate recombination of nonhomologous DNA fragments. Hence, the administration of cisplatin and irinotecan in tandem theoretically maximizes the antitumor effect of each drug.

Furthermore, the toxicity profile of cisplatin compliments that of irinotecan. Although both agents may cause myelosuppression, nausea, and vomiting, other toxicities of cisplatin are unique. Cumulative nephrotoxicity associated with cisplatin may be severe. Other major dose-related toxicities include ototoxicity and peripheral and autonomic neuropathy.

In vitro studies have substantiated a synergistic interaction between cisplatin and irinotecan. Masumoto et al demonstrated that the addition of SN-38 to cisplatin has no effect on cisplatin uptake or the rate of formation of interstrand DNA cross-links.[12] Instead, as quantified by the DNA-alkaline-elution technique, SN-38 significantly reduces the rate of removal of cisplatin-induced cross-links.

In the HST-1 human squamous-cell carcinoma, cell line peak synergy was achieved when cisplatin was given immediately prior to or simultaneously with SN-38.[13] Sequences in which SN-38 was given prior to cisplatin showed no statistical synergy. Masumoto et al concluded that peak synergy is achieved when the two drugs are given simultaneously, indicating sequence dependence.

Phase I and II studies evaluating the combination of irinotecan and cisplatin have been conducted primarily in non-small-cell lung cancer. Typically, these studies have employed a treatment schedule of irinotecan, 30 to 100 mg/m² on days 1, 8, and 15, followed by a 1-week rest period. Cisplatin has been dosed at 60 to 80 mg/m² on day 1 of each treatment cycle.

In four Japanese trials [14-17] in previously untreated patients with non-small-cell lung cancer, response rates have ranged from 43% to 54% (combined response, 49% [63 of 129 patients]). Dose-limiting toxicities were neutropenia and diarrhea. Nausea, vomiting, and fatigue were also frequently observed.

Clinical Studies of Irinotecan

Gastric Cancer

Kambe et al presented a late phase II study of irinotecan in patients with advanced gastric cancer.[18] Irinotecan was given weekly at a dose of 100 or 150 mg/m² every 2 weeks.

Of 81 patients enrolled, 60 were evaluable for response. The overall response rate was 14/60 (23%; 95% confidence interval [CI], 13% to 33%). No complete responses were noted. Of 45 previously treated patients, 9 (20%) responded to irinotecan, as did 5 (33%) of 15 untreated patients. Median duration of response was 2 months (range, 1 to 21 months). Of 76 patients (56 previously treated)
evaluable for toxicity, grade 2+ leukopenia was seen in 76%, nausea/vomiting in 42%, and diarrhea in 38%.

Recently, the Japanese National Cancer Center published two reports of monthly cisplatin and bimonthly irinotecan in metastatic gastric cancer. In a phase I-II study by Shirao et al, 24 patients were treated.[19] This study evaluated three dose levels, and established 70 mg/m² as the recommended dose of bimonthly irinotecan and 80 mg/m² as the recommended monthly dose of cisplatin. Irinotecan was administered first as a 90-minute infusion, followed 2 hours later by a 120-minute infusion of cisplatin.

Of 24 patients enrolled in this study, the majority of whom had received prior treatment, 10 patients achieved a partial response (42%; 95% CI, 22% to 62%) over three dose levels. Median time to response was 36 days, and median survival was 287 days.

Toxicity for the three dose levels was recorded. At dose level 2 (the recommended regimen), four (44%) of nine patients developed grade 3 neutropenia and one (11%) of nine patients experienced grade 3 diarrhea. No grade 4 toxicity was noted.

A second confirmatory study (using the above recommended regimen) by Boku et al enrolled 44 patients.[20] Major responses, including one complete response, were seen in 21 of 44 patients (48%; 95% CI, 33% to 63%). A superior response rate was observed in the 29 previously untreated patients, 17 of whom (59%; 95% CI, 41% to 77%) had a major response. Responses were seen at all sites, including the primary tumor (7/33; 21%), liver nodules (12/30; 40%), and lymph node disease (10/27; 37%). The median time to response was 40 days (range, 22 to 103 days). Major responders progressed at a median of 118 days (range, 41 to 253+ days). Median overall survival for the entire group was 309 days.

The incidence of grade 4 neutropenia was 22% per cycle and that of grade 3 or 4 diarrhea was 7% per cycle. Other toxicities were mild.

Confirmatory trials using a weekly cisplatin/irinotecan combination are currently under way at the University of Texas M. D. Anderson Cancer Center and at Memorial Sloan-Kettering Cancer Center (MSKCC).

Esophageal Cancer

**Single-Agent Irinotecan**---To date, no phase I or II studies have been published using single-agent irinotecan in esophageal cancer. A phase II trial at Dana-Farber Cancer Center is currently in progress.

**Weekly Irinotecan and Cisplatin**---A phase I study at MSKCC examined the combination of weekly irinotecan and cisplatin in patients with advanced solid tumor malignancies.[21] This schedule was developed to maximize the opportunity for synergy. Patients received 30 mg/m² of cisplatin over 30 minutes immediately followed by irinotecan over 90 minutes weekly for 4 weeks on days 1, 8, 15, and 22. Irinotecan was started at 50 mg/m²/wk and then escalated by 30% increments. The maximum tolerable dose was 50 mg/m²/wk for previously treated patients and 65 mg/m²/wk for untreated patients. One cycle was defined as four weekly treatments followed by a 2-week rest period.

Neutropenia was the main dose-limiting toxicity; other toxicities were minimal. Encouraging antitumor activity was noted, including a partial response lasting 5 months in one patient with a gastroesophageal junction tumor metastatic to the liver.

Based on this experience, our group at MSKCC is currently conducting a phase II trial of weekly cisplatin and irinotecan in unresectable, locally recurrent, or metastatic esophageal cancer. Patients with adenocarcinoma or squamous cell carcinoma are being enrolled. These patients have had no prior chemotherapy or radiotherapy and have adequate renal, hematologic, and hepatobiliary function.
Of 29 patients entered to date, 21 are evaluable for response. Patient demographics, outlined in Table 1, are similar to those in previous trials conducted by our group. The typical patient is a middle-aged man with previously untreated adenocarcinoma and excellent performance status.

The preliminary major response rate of 53% in this trial, including one complete response, compares favorably to results achieved with cisplatin-5-FU or single-agent paclitaxel (Taxol) therapy (see Table 2). Similar response rates to irinotecan and cisplatin have been seen in patients with adenocarcinoma and squamous cell carcinoma. Most patients have required only one cycle to achieve a response. Median response duration and patient survival are yet to be determined.

Toxicity has been relatively mild. Approximately 25% of patients have developed moderate myelosuppression (primarily neutropenia), and approximately 25% have experienced mild nausea, fatigue, and diarrhea. No unexpected toxicities have been seen.

Dose intensity is preserved, with patients receiving 120 mg/m² of cisplatin and 260 mg/m² of irinotecan over a 6-week period. This compares favorably with other cisplatin-irinotecan combinations found in the literature.

Quality of life is being assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) scales. The palliative effect of this regimen appears to be significant, with the majority of patients showing improvement or resolution of dysphagia after one cycle of therapy.

Conclusions and Future Directions

Irinotecan is an active drug in upper gastrointestinal malignancies. Preclinical data have demonstrated the synergy of the combination of cisplatin and irinotecan, and phase I trials have shown that it is safe.

Phase II trials of irinotecan and cisplatin in gastric cancer conducted in Japan have indicated a high degree of antitumor activity. Confirmatory trials are under way in the United States.

Preliminary results from our ongoing phase II trial in esophageal cancer suggest significant response to the cisplatin-irinotecan combination. Ultimately, this regimen will need to be compared with other cisplatin-containing protocols in multicenter phase III trials. Neoadjuvant studies may also be considered.

A priority in future clinical trials will be to add another agent to the cisplatin-irinotecan regimen. In esophageal cancer, paclitaxel is a logical first choice, given its high single-agent response rate. Myelosuppression remains a significant concern, however, as demonstrated in phase I trials combining paclitaxel with cisplatin[22,23] or docetaxel (Taxotere) with irinotecan.[24] Neuropathy may also become dose-limiting. Moreover, in vitro studies in the paclitaxel-resistant A2780 human ovarian cancer cell line suggest antagonism between paclitaxel and irinotecan.[25] However, this antagonism has not been seen in phase I trials of paclitaxel and topotecan[26] or docetaxel and irinotecan.[24]

In the HST-1 human squamous carcinoma cell line, 5-FU has shown synergy with both cisplatin and irinotecan.[13] Multiple phase II trials have demonstrated in vivo synergy of cisplatin and 5-FU. The combination of weekly irinotecan, 5-FU, and leucovorin has been well studied[27] and is currently being evaluated in a phase III trial in metastatic colorectal carcinoma.

In gastric cancer, the efficacy of 5-FU is established, and its use in combination with cisplatin and irinotecan appears to be of interest. In esophageal cancer, the possible synergistic benefits of 5-FU and its likely superior toxicity profile will need to be weighed against the superior antitumor effect of paclitaxel in any future phase I trials.
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