Cisplatin and Irinotecan in Upper Gastrointestinal Malignancies

By Eileen M. O'Reilly, MD [2] and David H. Ilson, MD, PhD [3]

Irinotecan (CPT-11, Camptosar) a topoisomerase I inhibitor derived from the Chinese shrub Camptotheca acuminata, has broad activity in varied gastrointestinal malignancies, including pancreatic, biliary, esophageal

Introduction

Esophageal and gastric cancers are relatively uncommon in the United States; however, both are associated with high case fatality rates, underscoring their poor prognosis and increasing the relative importance of both malignancies. In the year 2001, 13,200 new cases of esophageal cancer are anticipated, with approximately 90% of patients expected to succumb to their disease.[1] For stomach cancer, 21,700 new patients are expected to be diagnosed this year.[1] The majority of these patients will have locally advanced or metastatic disease, which is associated with a short median survival time. For both diseases, complete surgical resection with negative margins offers the best prospect for long-term disease control. This is achievable in only a minority of patients, however, and even when achieved, the majority of patients experience a recurrence of disease.

Median survival of patients diagnosed with metastatic disease is typically significantly less than 1 year. Major treatment goals for such patients include symptom palliation and quality-of-life improvements, as well as prolongation of median survival. The optimal therapy for advanced esophagogastric malignancies has not been defined. Cisplatin (Platinol) and fluorouracil (5-FU)-based combinations are often used for both diseases; however, superiority in the treatment of gastric cancer has not been demonstrated over other drug combinations, eg, etoposide/leucovorin/fluorouracil (ELF),[2] emerging taxane-based combinations,[3-5] or indeed, single-agent therapy.[6]

The camptothecins, a novel class of chemotherapeutic agents derived from the Camptotheca acuminata tree, act by inhibiting topoisomerase I.[7] Irinotecan (CPT-11, Camptosar) is a semisynthetic, water-soluble camptothecin that has a more favorable toxicity profile than its parent compound camptothecin. Irinotecan also has a broad spectrum of activity in both non-small-cell and small-cell lung cancers, colorectal, gastric, esophageal, pancreatic, and ovarian malignancies.[8,9]

Irinotecan is a prodrug that is converted by carboxylesterases to its active metabolite SN-38. A topoisomerase I/DNA cleavable complex is formed that is stable and inhibits reannealing of parent DNA, effecting irreversible double-strand DNA breaks. This ultimately results in cell death.

Cisplatin/Irinotecan Combination

Cisplatin is an alkylating agent with a long-established role in treating upper gastrointestinal malignancies.[10,11] Cisplatin forms a platinum bond with DNA and RNA, resulting in alteration of the conformation of the DNA helix and, ultimately, cell death. In vitro data from Masumoto et al[12] suggest that the cisplatin/irinotecan combination is synergistic, with optimal activity when cisplatin is administered prior to irinotecan or SN-38.[13] Several hypotheses have been proposed to explain this synergy, although the exact mechanisms have not been well defined. Masumoto et al[14] and Fukuda et al[15], in independent experimental preclinical models, have suggested that when cells are treated with SN-38 in addition to cisplatin, greater amounts of cross-linked DNA result. These effects were evident 1 to 2 days following cisplatin washout, suggesting possible interference with a DNA repair protein that removes cisplatin-induced DNA adducts.

Saltz and colleagues[16] at Memorial Sloan-Kettering Cancer Center (MSKCC) conducted the first US clinical trial of cisplatin and irinotecan using a weekly schedule for both drugs, ie, once a week for 4 weeks with cycles repeated every 6 weeks. This study builds on the US data regarding single-agent

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Cisplatin/Irinotecan in Esophageal Cancer

Ilson and colleagues recently reported results of a phase II study of cisplatin and irinotecan in metastatic esophageal cancer.[17] Cisplatin at 30 mg/m² and irinotecan at 65 mg/m² were given weekly on days 1, 8, 15, and 22, followed by 2 weeks of rest, to patients with previously untreated, measurable metastatic adenocarcinoma or squamous cell cancer of the esophagus. The primary study end point was response rate, and secondary end points were toxicity, survival, dysphagia relief, and quality of life for the combination. Quality of life was assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C-30 instrument. Dysphagia was evaluated using a published dysphagia scale.

A total of 35 patients—23 with adenocarcinoma and 12 with squamous cell cancer—were treated. The median patient age was 57 years and the median Karnofsky performance status was 80%. Almost 50% of the patients had liver metastases. Eighteen patients (51%) had a partial response to treatment and two patients (6%) had a complete response, for an overall objective response rate of 57%. An additional seven patients (20%) had a minor response and seven had stable disease (20%). Thus, tangible benefits from the two-drug combination were apparent in the majority of patients. The median actuarial survival for the population was an encouraging 14.6 months. Response rates among patients with squamous cell cancer and adenocarcinoma were similar, ie, 66% and 52%, respectively.

Palliation of dysphagia is a primary goal of palliative treatment in esophageal cancer. The cisplatin/irinotecan combination led to complete dysphagia relief in 14 (70%) of 20 evaluable patients with dysphagia. An additional four patients (20%) had some, although incomplete, dysphagia relief. These benefits were evident after a median of one 6-week treatment cycle.

Toxicities from the cisplatin/irinotecan combination were primarily myelosuppression and gastrointestinal effects, similar to those observed in the original phase I study of the combination. Grade 3/4 neutropenia was evident in 46% of patients, but only one episode of neutropenic fever was observed. Four patients (11%) had grade 3 diarrhea, but none had grade 4 diarrhea or required hospitalization for diarrhea. Two patients (6%) experienced grade 3 nausea/vomiting and one patient (3%) grade 3 fatigue.

A similar study of cisplatin and irinotecan in patients with gastric cancer was just completed.[18] Entry criteria included measurable metastatic disease and no previous therapy. Eighteen patients were enrolled, with a median age of 54 years and a median performance status of 80%. Response rates were lower than those in the esophageal population, with an overall major objective response rate of 33% (six partial responses). Toxicity was also more severe, with one treatment-related death and six patients (33%) requiring hospitalization for management of toxic effects. The difference between these two patient populations may be that the gastric cancer patients were sicker than those with esophageal cancer. Ajani and colleagues[19] reported similar results for the two-drug combination in gastric and gastroesophageal-junction cancers.

The weekly schedule of cisplatin/irinotecan offers a new option for treating advanced upper gastrointestinal cancers. The activity and tolerability of this two-drug combination supports its use as the backbone of regimens that include other chemotherapeutic agents or radiation, which are being assessed in ongoing studies.

Phase I Triplet Studies of Triple Therapy Including Cisplatin/Irinotecan
Both paclitaxel (Taxol)[20,21] and 5-FU[11] have established activity in esophageal and gastric cancers and are obvious drugs to consider for combinations with the cisplatin/irinotecan doublet in attempts to enhance response rates and treatment benefits. A major issue pertaining to three-drug combinations is clinical trial design, in particular dosing and schedule. The key concerns in this regard are the greater potential for toxicity and for compromising doses of key drugs.

Two phase I trials being conducted at MSKCC will determine the recommended phase II doses for two three-drug combinations: cisplatin/irinotecan/paclitaxel and cisplatin/irinotecan/5-FU. In both trials, the backbone is cisplatin and irinotecan given on days 1, 8, 15, and 22 followed by a 2-week rest, with cycles requested every 6 weeks. In the first study, paclitaxel is administered as a 1-hour weekly infusion combined with cisplatin at 30 mg/m$^2$ and irinotecan at 50 mg/m$^2$. The paclitaxel dose-escalation scheme tests 40, 50, 65, and 80 mg/m$^2$. Sixteen patients have been treated. Accrual continues at the paclitaxel dose of 65 mg/m$^2$ (see Table 1 and Table 2).

In the second study, 5-FU is combined with cisplatin and irinotecan. The cisplatin dose is 30 mg/m$^2$ and doses of both irinotecan and 5-FU are escalated. The irinotecan starting dose is 40 mg/m$^2$, with other cohorts receiving 50, 65, and 80 mg/m$^2$. The starting 5-FU dose is 425 mg/m$^2$, with one planned dose escalation to 500 mg/m$^2$. Thus far, six patients have been enrolled (see Table 3 and Table 4), all at the first dose level (irinotecan at 40 mg/m$^2$, 5-FU at 425 mg/m$^2$) in view of a dose-limiting toxicity (prolonged neutropenia). In both of these trials, significant activity has been demonstrated in patients with upper gastrointestinal malignancies. Dose escalation continues in both studies and the recommended phase II doses remain to be defined.

**Cisplatin/Irinotecan and Radiation**

Irinotecan has demonstrated significant radiation-enhancement properties in several preclinical studies.[22-24] Radiosensitization for this drug appears to be dose- and schedule-dependent as well as S-phase-dependent.[24,25] Irinotecan inhibits radiation-induced DNA damage repair mechanisms, although the precise method of radiation potentiation is not well understood.[26] Several centers are examining radiation/irinotecan combinations.

A phase I study underway at MSKCC is assessing cisplatin/irinotecan and radiation in patients with locally advanced unresectable or resectable esophageal cancers. Patients with resectable malignancies are receiving the treatment as neoadjuvant therapy, with the option for surgical resection on completion of the combined-modality part of the program. The study consists of two parts: induction chemotherapy and combined-modality chemoradiation. Induction chemotherapy consists of weekly cisplatin and irinotecan for 4 weeks to effect dysphagia relief and to allow for radiation planning. Following 2 weeks of rest, the combined-modality therapy commences. Radiation is administered at standard dose and fractionation, 180 cGy/d, 5 days a week, for 28 fractions. Cisplatin and irinotecan are administered on day 1 of weeks 1, 2, 4, and 5, with a rest from chemotherapy on week 3 of radiation when myelosuppression is anticipated to occur.

The cisplatin dose is fixed at 30 mg/m$^2$ and irinotecan is dose-escalated during the radiation in successive patient cohorts starting at 40 mg/m$^2$ and increasing to 50, 60, 80, and 100 mg/m$^2$. Currently, dose escalation continues at the 65 mg/m$^2$ dose level. Only preliminary data are available; however, of three evaluable patients at the first dose level (irinotecan at 40 mg/m$^2$), two have undergone surgery and have had a pathologic complete response to therapy. Both patients had endoscopically staged T3 tumors before treatment. The maximum tolerated dose of irinotecan that can be administered with cisplatin and radiation remains to be defined.

The combination of irinotecan and radiation is also being extensively tested in lung cancer patients.[27-29] Elsewhere in this publication, Ajani and colleagues from M. D. Anderson Cancer Center report on their experience with irinotecan and radiation in patients with locally advanced upper gastrointestinal malignancies. Researchers at Vanderbilt University are conducting a phase I study of the irinotecan, carboplatin (Paraplatin), and radiation combination.

**Conclusions**
The cisplatin/irinotecan combination is now an established regimen for treating esophageal,[17] gastric,[30,31] and lung cancers.[32,33] Encouraging activity and tolerable toxicity have been observed in all of these malignancies. Exciting new developments in the treatment of upper gastrointestinal malignancies include developing regimens with this doublet combined with radiation and with other new or established chemotherapeutic agents, such as the taxanes. The ultimate goal is to define new neoadjuvant and adjuvant regimens that will result in higher response rates and a greater potential for treating microscopic disease and effecting long-term disease control in esophageal and gastric cancers.

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**References:**


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