Irinotecan Plus Cisplatin in Advanced Gastric or Gastroesophageal Junction Carcinoma

By Jaffer A. Ajani, MD [2], Jackie Baker, RN [3], Peter W. T. Pisters, MD [4], Linus Ho, MD, PhD [5], Barry W. Feig, MD [6], and Paul F. Mansfield, MD [7]

A phase II study was conducted to assess the response rate and toxicity profile of the combination of irinotecan (CPT-11, Camptosar) and cisplatin (Platinol) administered weekly to patients with untreated advanced gastric or gastroesophageal adenocarcinoma.

Introduction

Gastric carcinoma continues to be a significant health problem despite its declining incidence. Gastric carcinoma is the leading cause of cancer-related death in many countries. In 2001, it is estimated that there will be 21,700 new cases of gastric carcinoma in the United States and 12,800 deaths are expected.[1] Although advanced disease remains incurable, chemotherapy can be palliative. Compared with the best supportive care alone, combination chemotherapy improved quality of life and overall survival in four small randomized trials.[2-5] New classes of agents that have shown some degree of activity against gastric and esophageal adenocarcinomas include topoisomerase I inhibitors and taxanes. Among the topoisomerase I inhibitors, irinotecan (CPT-11, Camptosar) is of particular interest due to its activity against these tumors.[6,7]

Phase II Study of Weekly Irinotecan/Cisplatin

We conducted a phase II study of the combination of irinotecan and cisplatin (Platinol) administered on a weekly schedule to patients with previously untreated advanced gastric carcinoma.

Patients and Methods

Patients with histologically proven advanced gastric or gastroesophageal adenocarcinoma were eligible for inclusion in the study. Patients needed to have measurable carcinoma. Normal bone marrow, liver, and renal functions, life expectancy of more than 3 months, and a performance status (Zubrod scale) of 2 or less were also required. All patients provided a written informed consent. As part of the pretreatment evaluation, a complete blood cell count, multichannel chemical survey, and electrolyte measurement were performed. All patients underwent computed tomography of the abdomen and pelvis (if indicated), chest radiography, and other imaging studies if necessary. A complete history was obtained and a physical examination was performed prior to study entry.

Chemotherapy was administered in the outpatient setting. All patients received hydration before and after receiving cisplatin. Premedication consisted of intravenous (IV) dexamethasone, lorazepam, and ondansetron (Zofran) to prevent emesis. Patients received extensive verbal and written instructions regarding early institution of therapy for diarrhea. Patients also received oral medications to reduce the severity of delayed nausea and vomiting, and loperamide to reduce the severity of diarrhea.

Chemotherapy consisted of 65 mg/m² of irinotecan IV given over 90 minutes followed by 30 mg/m² of cisplatin IV over 60 minutes. Both drugs were administered 1 day per week for 4 consecutive weeks, followed by a 2-week recovery period. Thus, one cycle was 6 weeks in duration (4 weeks of treatment and 2 weeks of recovery).

Response was evaluated after the first, second, and fourth cycles, and every two cycles thereafter. Patients continued therapy until there was evidence of progressive disease or unacceptable toxicity.
Standard toxicity and response assessment criteria were used. It was believed that a response rate of at least 30% would justify continuing and expanding the trial in the future. An optimal two-stage Simon design[8] was used to determine the exact number of patients to be accrued. The hypotheses were that $H_0: P \leq P_0 (0.10)$ vs $H_1: P \geq P_1 (0.30)$ with $\alpha = 0.05$ and $\beta = 0.10$ (90% power). Thus, a total of 35 evaluable patients were to be accrued in the study.

**Results**

A total of 38 patients were entered in the study. The median age was 58.5 years (range: 20 to 75 years). Twenty-nine (76%) of 38 patients had poorly differentiated carcinoma and most patients (76%) had a primary carcinoma located in the proximal portion of the stomach.

Thirty-six of 38 patients (95%) were assessable for response and toxicity. A total of 98 treatment cycles were administered; the median number of 6-week cycles per patient was 2.5 (range: 1 to 7 cycles). A total of 353 (93%) of the planned 380 weekly doses were administered. Twenty-five patients required granulocyte colony-stimulating factor support after the first chemotherapy cycle. Twenty-seven (7%) of 380 planned weekly doses were canceled because of toxicity, and 52 (15%) of 353 weekly doses were delayed for the same reason. Fifty-three (66%) of the 79 delayed or canceled weekly doses occurred at the time of the third or fourth week of treatment.

Among 36 evaluable patients, the overall response rate was 58%: 4 (11%) patients had a complete response and 17 (47%) had a partial response (see Table 1). Five patients (14%) had a minor response, 8 (22%) had progressive disease during therapy, and 2 (6%) had stable disease. Median time to disease progression was 24 weeks (95% confidence interval [CI]: 16 to 32 weeks), and median survival of all 36 patients was 9 months (95% CI: 7.5 to 10.5 months; range: 1 to 23+ months).

There was one treatment-related death: an elderly woman died of neutropenic sepsis associated with multiple organ failure. The major toxic effects were diarrhea, neutropenia, and fatigue. It is interesting to note that patients or caretakers reported higher grades of diarrhea in the first or second treatment cycle than in later courses. A possible explanation is that patients may not have followed instructions for this toxic effect until they had experienced severe diarrhea. Severe diarrhea was less common in the subsequent cycle.

**Discussion**

Results of this study demonstrate that irinotecan in combination with cisplatin is active in previously untreated patients with advanced gastric carcinoma. Irinotecan has been shown to have single-agent activity against gastric carcinoma. For example, data from Japan showed that single-agent irinotecan was active in patients with treated and untreated gastric carcinoma.[6] Results of a recent European study showed that 17% of 34 previously untreated patients with gastric carcinoma responded to single-agent irinotecan.[7]

Irinotecan in combination with cisplatin has also been studied in Japan, with demonstrated response rates greater than 40%.[9,10] In both of these Japanese phase II studies, cisplatin was administered every 4 weeks and irinotecan every 2 weeks. Shirao et al[9] reported a 42% response rate among 24 previously untreated patients with advanced gastric carcinoma who received irinotecan plus cisplatin. The major toxic effect was neutropenia. In the study by Boku et al,[10] a 59% response rate was observed among 29 previously untreated patients who received irinotecan plus cisplatin. The major toxic effects were neutropenia and diarrhea.

In the study reported herein, which included the largest group of untreated patients studied thus far, we used a different treatment schedule from that developed by the Japanese investigators. Both drugs were administered 1 day per week for 4 consecutive weeks followed by a 2-week recovery period. This schedule was based on results described by Saltz et al,[11] which showed that the schedule was well tolerated by patients with advanced gastrointestinal carcinoma. The combination of irinotecan plus cisplatin administered according to this schedule resulted in a response rate of 52% in 23 untreated patients with adenocarcinoma of the esophagus.[12]
We observed that 66% of all delays or cancellations of weekly doses occurred at the time of the third or fourth weekly dose. The delays or cancellations were predominantly caused by unresolved diarrhea, fatigue, or neutropenia, which increased the hardship on the patients and/or increased the cost of care. Therefore, we are conducting a study in which both agents are administered 1 day per week for 2 weeks, followed by 1 week of recovery. Thus, patients still receive four doses in a 6-week cycle; however, the 2-week recovery period has been divided. It is our hypothesis that cisplatin may contribute to excessive fatigue; thus, either the cisplatin dose may be reduced or cisplatin may be replaced by other agents. Further investigations would be of interest.

**Conclusion**

In conclusion, the combination of irinotecan and cisplatin is active in advanced gastric or gastroesophageal junction carcinoma. Further developments in Japan and Europe will help to define the role of this agent in the overall treatment approach to this disease. Additional investigations of irinotecan combined with other active agents and with radiotherapy are warranted.

**References:**


