Irinotecan/Cisplatin in Advanced, Treated Gastric or Gastroesophageal Junction Carcinoma

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We conducted a phase II study to assess the response rate and toxicity profile of the irinotecan (CPT-11, Camptosar) plus cisplatin combination administered weekly to patients with at least one previous chemotherapy for advanced adenocarcinoma of the stomach or gastroesophageal junction. Patients with histologic proof of adenocarcinoma of the stomach or gastroesophageal junction with adequate liver, kidney, and bone marrow functions were treated with 50 mg/m² of irinotecan plus 30 mg/m² of cisplatin, both administered intravenously 1 day a week for 4 consecutive weeks, followed by a 2-week recovery period.

Gastric carcinoma continues to be a significant health problem despite its decreasing incidence. It remains the second most common malignant disorder in the world, accounting for more than 750,000 new cases and more than 500,000 deaths each year.[1] It is the number 1 cause of cancer-related death in many countries. Although the incidence of gastric carcinoma is one of the lowest of all malignancies in North America, gastric carcinoma is the eighth leading cause of cancer death in the United States. It was estimated that in 2002, there would be more than 21,600 new cases of gastric carcinoma in the United States and 12,400 deaths.[2] At the time of diagnosis, approximately 50% of gastric carcinoma patients have metastatic disease.[2]

Although advanced disease remains incurable, chemotherapy can be palliative. Compared with best supportive care alone, combination chemotherapy improved quality of life and overall survival in four small randomized trials.[3-6] Once patients have not responded to front-line chemotherapy (often fluorouracil- or cisplatin-based), there is no established second-line chemotherapy for these patients. The combination of irinotecan (CPT-11, Camptosar) and cisplatin has demonstrated activity as first- and second-line therapy for gastric carcinoma.[7] We performed a phase II trial of this regimen using a previously established treatment schedule[8] in patients who have had at least one previous systemic chemotherapy. Preliminary results are presented here.

Patients and Methods

Patients with histologic proof of advanced gastric or gastroesophageal adenocarcinoma, with measurable disease, were eligible for inclusion in the study. They were required to have an absolute granulocyte count of 1,500/µL or more, a hemoglobin level of 8 g/dL or more, and a platelet count of 100,000/µL or more; serum bilirubin level of 1.5 mg/dL or less, serum creatinine level of 1.5 mg/dL or less; life expectancy of more than 3 months; and a performance status of 2 or less on the Zubrod scale. Patients must have received at least one previous chemotherapy regimen (that did not include a topoisomerase I inhibitor). The Institutional Review Board approved the study, and all patients provided written informed consent.

Pretreatment evaluation included a complete blood cell count, multichannel chemical survey, and electrolyte measurement. 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 consisted of 50 mg/m² of irinotecan given intravenously (IV) 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 recovery period of 2 weeks. Thus, one cycle was 6 weeks long (4 weeks of therapy and 2 weeks of recovery).

Chemotherapy was administered in the outpatient setting. All patients received hydration before and after the cisplatin, and were premedicated with IV dexamethasone, lorazepam, and ondansetron (Zofran) to prevent emesis. Patients received extensive verbal and written instructions regarding early therapy for diarrhea; they were given oral medications to reduce the severity of delayed
nausea and vomiting, and loperamide to reduce the severity of diarrhea. Standard response and toxicity definitions were used.

**Results**

Characteristics of the 32 patients entered in the study are outlined in Table 1. Median age was 50 years; median performance status was 1 (range: 0-2). Table 2 shows chemotherapies patients had received previously.

Among 29 patients assessable for response and toxicity, 9 (31%) had partial responses. Time to progression was 7 weeks (range: 5-48+ weeks), and the median overall survival time was 5 months (range: 2.5-31 months).

No treatment-related deaths occurred. Observed toxicities are listed in Table 3. A total of 46 of 260 doses in 65 6-week courses were either delayed or missed. Most of the delayed or missed doses occurred in the third or fourth week of the cycle.

**Discussion**

Our results showed that irinotecan plus cisplatin is an active combination in previously treated patients with advanced gastric carcinoma. Irinotecan has single-agent activity against gastric carcinoma, as shown in data from Japan involving patients with treated and untreated gastric carcinoma.[9] The 31% response rate achieved in our study is consistent with results obtained in other phase II studies[10,11] and reaffirms the activity of irinotecan plus cisplatin. The median survival of 5 months (in the second-line therapy setting) may be considered quite reasonable, yet the survival end point is more appropriately addressed in a phase III trial than in a phase II trial. Activity of this combination in untreated patients has been reported.[7] There is no established second-line therapy for patients with advanced gastric carcinoma, yet many patients who qualify for first-line therapy are still in good physical condition when second-line therapy becomes necessary. We propose a phase III trial comparing best supportive care (or any phase I study) vs irinotecan plus cisplatin in patients in whom first-line therapy has failed. As previously emphasized, the schedule of this regimen needs to be modified to improve patient tolerability.

**References:**


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