Both irinotecan (CPT-11, Camptosar) and paclitaxel have been shown to have single-agent activity in adenocarcinomas of the esophagus and gastric cardia. A phase I trial of the combination at UCLA established the dose as irinotecan at 225 mg/m² and paclitaxel at 100 mg/m² every 3 weeks. Preliminary data from a phase II trial of this regimen in adenocarcinomas of the gastroesophageal junction show good tolerability and promising activity (response rate of 27%), even in previously treated patients.

A previously treated patients, adenocarcinomas of the gastroesophageal junction comprise adenocarcinomas of the esophagus and gastric cardia. The cancers are quite similar histologically and epidemiologically, and they are different from either squamous cell carcinoma of the esophagus or the more frequent distal adenocarcinoma of the stomach. The etiology of these malignancies remains obscure, but they appear to be related to chronic gastroesophageal reflux and intestinal metaplasia. The epidemiology and natural history of adenocarcinomas of the gastric cardia appear to be much more similar to that of adenocarcinoma of the esophagus than that of the distal stomach. Large tumors of the gastroesophageal junction, it is difficult to distinguish between esophageal and gastric origin. Once quite rare, these cancers are the most rapidly increasing solid tumors in the United States and Western Europe, and now account for more than 50% of esophageal carcinomas and an increasing number of gastric malignancies. Unfortunately, most patients’ cancers are not resectable at the time of diagnosis or relapse after surgery. The standard of care has historically consisted of combinations of fluorouracil (5-FU) and cisplatin. Although response rates are reasonable in the 20% to 30% range survival remains relatively limited (6 to 11 months), and the toxicity of treatment, particularly from the cisplatin, can be severe in these fragile patients. The limitations of standard therapy has led to the study of newer agents in adenocarcinomas of the gastroesophageal junction, including taxanes and topoisomerase I inhibitors. Paclitaxel may be the most active single agent in gastroesophageal malignancies, with Ajani et al reporting a response rate of 34% in adenocarcinoma of the esophagus. Combinations of paclitaxel with cisplatin and 5-FU have also resulted in significant response rates of 48% to 51%. The topoisomerase I inhibitor irinotecan (CPT-11, Camptosar) possesses activity in a number of adenocarcinomas, including those of the colon and lung. Single-agent response rates of 14% in adenocarcinoma of the esophagus and 15% in esophageal and gastric carcinomas have lead it to be used in combination with 5-FU/leucovorin and cisplatin, where respective response rates of 22% in gastric adenocarcinoma and 57% in advanced esophageal cancer (52% adenocarcinoma, 66% squamous carcinoma) were reported. The mostly nonoverlapping toxicities and different mechanisms of action of irinotecan and paclitaxel led to the examination of this combination in a phase I setting by Rosen et al. No significant drug interactions were seen and the combination was quite tolerable, with neutropenia being the dose-limiting toxicity with some activity seen in upper gastrointestinal tract cancers. Therefore, the regimen was taken forward into a phase II trial in adenocarcinomas of the gastroesophageal junction.
**Study Design**

**and Patient Population** The protocol was approved by the UCLA, OHSU, Northwestern University, and USC institutional review boards. The study was a single-arm multicenter phase II study. The primary end point was response rate and secondary end points were safety and survival. A two-stage Simon design was used to calculate sample size. [13] If one response in the first 13 patients was seen then the study was to accrue an additional 14 patients. Patients with histologically proven adenocarcinoma of the esophagus or gastric cardia were eligible for the trial. Documentation of the location of the tumor by endoscopy or radiologic study was required. The patients had to have bidimensionally measurable disease and adequate hematologic, liver, and renal function. Patients required an Eastern Cooperative Oncology Group performance status of > 2. Patients who had received more than one prior treatment regimen for metastatic disease, were receiving antiepileptic medication, and had known Gilbert’s syndrome were excluded. Patients had screening laboratories, computed tomography (CT) of the chest, abdomen, and pelvis, and a history and physical prior to the start of treatment. **Methods** Patients received pretreatment with dexamethasone at 20 mg IV, diphenhydramine at 50 mg IV, famotidine at 20 mg IV (or similar H₂ receptor antagonist), and granisetron (Kytril) at 1 mg IV (or similar 5HT₃ antagonist). After pretreatment, patients were treated with irinotecan at 225 mg/m² over 90 minutes followed by paclitaxel at 100 mg/m² over 3 hours every 3 weeks. Atropine was administered as needed for cholinergic symptoms. Patients were counseled on the use of, and provided with, high-dose loperamide in case of diarrhea. Response was determined every three cycles (9 weeks) using CT or magnetic resonance imaging (MRI) scans using

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Response Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>6  27%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6  27%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>10 45%</td>
</tr>
<tr>
<td>Nonevaluable</td>
<td>5  –</td>
</tr>
</tbody>
</table>

*Of evaluable patients.
the World Health Organization criteria. Responses had to be verified on another radiologic study at least 4 weeks later, though there was no provision for early scans as part of the protocol. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 2.0. **Results** A total of 27 patients were enrolled onto the study; see Table 1 for the demographics. Median age was 62 years (range: 45-82 years). The striking male predominance (85%) is consistent with the epidemiology of adenocarcinomas of the gastroesophageal junction. Eight patients had prior treatment for their cancer, including some receiving more than one treatment modality. At this time, 22 patients are evaluable for response. The median number of treatment cycles was 3 (range: 3-20 cycles) and median survival was 8.6 months (range: 2-24+ months). The documented partial response rate was 27%, with 27% of patients having stable disease (Table 2). Half of the pretreated patients were evaluable had partial responses (3 of 6). Toxicity was manageable, with three admissions for neutropenic fevers. In the 16 patients with complete toxicity data representing 110 cycles, only nine grade 3 and one grade 4 neutropenia were reported. Diarrhea was uncommon with only three reports of grade 3 and none of grade 4.

**Discussion** The proper treatment of advanced carcinoma of the gastroesophageal junction remains unclear. Clearly, irinotecan and paclitaxel are both active agents in this disease, and their combination appears to have significant activity, even in previously treated patients. While single-agent paclitaxel possesses activity, this is at the cost of significant neutropenia that may require the use of growth factors.[5] Other combinations using these drugs may have gastrointestinal and bone marrow toxicity.[7] This regimen is convenient and well tolerated with minimal neutropenia and diarrhea. In addition to collecting clinical data, we plan to examine molecular correlates including UDP-glucuronosyltransferase (UGT) 1A1 polymorphisms[14] and beta-tubulin III isoform levels[15] potentially to help identify, respectively, both patients at increased risk of toxicity, and tumors less likely to respond to taxanes.

**Disclosures:** The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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