Irinotecan, Cisplatin, and Radiation in Esophageal Cancer

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The limited effectiveness of currently available chemotherapy in the treatment of advanced esophageal cancer, and the poor survival achieved in locally advanced disease with combined chemoradiotherapy with or without surgery, have prompted the evaluation of new agents. Irinotecan (CPT-11, Camptosar) has promising single-agent activity in gastrointestinal cancers.

Esophageal carcinoma is an aggressive cancer with a poor prognosis. In 2002, 13,100 Americans will be diagnosed with esophageal cancer, and more than 95% of these patients will die of their disease.[1] Half of patients present with overt metastatic disease, with a median survival of usually less than 1 year. The remaining half of patients present with locally advanced disease potentially amenable to surgical- or radiation-based therapy. Because of the relative rarity of esophageal cancer and the absence of effective screening, most patients present with symptomatic dysphagia and usually have locally advanced, transmural, or lymph-node-positive disease.

Despite treatment with surgery, definitive chemoradiotherapy, or combined preoperative chemoradiotherapy followed by surgery, 5-year survival rates of less than 20% to 35% are generally achieved.[2-5] The poor survival in locally advanced disease is due to a high incidence of both distant, metastatic disease recurrence and local disease recurrence. Conventional chemotherapy combining a continuous infusion of fluorouracil (5-FU) and cisplatin is associated with substantial toxicity, including stomatitis, diarrhea, nausea, fatigue, and myelosuppression. The severe mucosal and gastrointestinal toxicities that occur when concurrent radiotherapy is combined with 5-FU and cisplatin have led many investigators to mandate the placement of enteral feeding tubes in patients prior to therapy. The toxicity and limited effectiveness of currently used cytotoxic chemotherapy, either to palliate metastatic disease or used in combination with radiotherapy in locally advanced disease, have mandated the ongoing investigation of newer cytotoxic agents in esophageal cancer.

**Irinotecan**

Irinotecan (CPT-11, Camptosar), a semisynthetic camptothecin, has emerged as a significant new cytotoxic agent with a broad spectrum of antitumor activity. Early trials in Japan indicated promising antitumor activity for irinotecan in a number of gastrointestinal malignancies, including colorectal, pancreatic, and gastric cancer. Irinotecan has a novel mechanism of action. Once it is converted to its active metabolite SN-38, irinotecan binds to the complex of the enzyme topoisomerase I and DNA, stabilizing the cleavable complex and inhibiting reannealing of parent DNA. [6-9] Single-strand DNA breaks are converted to irreversible double-strand breaks when a DNA replication fork encounters a cleavable complex, leading to cell death.[7-9] Phase II evaluation of irinotecan in gastric cancer in Japan indicated a single-agent response rate of 20% to 30%.[10] Recent American trials of single-agent irinotecan, given at a weekly dose of 125 mg/m², 4 weeks on and 2 weeks off treatment, indicate modest single-agent activity with a response rate of 15% in gastric and gastroesophageal junction cancer.[11,12]

**Irinotecan and Cisplatin**

Cisplatin is an alkylating agent commonly used in combination chemotherapy for upper gastrointestinal malignancies. Cisplatin acts through a mechanism different from that of irinotecan, forming platinum adducts with DNA leading to inhibition of DNA synthesis and repair. In vitro, cisplatin and irinotecan have demonstrated sequence-dependent synergy in a variety of cancer cell lines. Peak synergy appears to be achieved in cell lines when cisplatin is given immediately prior to or in combination with SN-38.[13,14] One potential mechanism of synergy between cisplatin and irinotecan is for SN-38 to reduce the rate of removal of cisplatin-induced DNA interstrand cross-links.[15,16] Cisplatin may also increase SN-38 inhibition of topoisomerase I.[16] Saltz et al conducted a phase I trial combining weekly irinotecan and cisplatin.[17] The weekly schedule was developed to optimize potential synergy between the two agents. Patients received...
cisplatin over 30 minutes immediately followed by irinotecan over 90 minutes weekly, for 4 consecutive weeks, followed by a 2-week rest; this 6-week period comprised one treatment cycle. Neutropenia was the dose-limiting toxicity; other toxicities were minimal, and included manageable diarrhea, nausea, and fatigue. Doses recommended for phase II studies in previously untreated patients were cisplatin at 30 mg/m² and irinotecan at 65 mg/m².

Ilson and colleagues subsequently performed a phase II trial of weekly cisplatin and irinotecan in patients with metastatic esophageal cancer, using the weekly schedule.[18] A response rate of 57% was observed in 35 patients. The median response duration was 4.2 months, and median actuarial survival was 14.6 months. Dysphagia relief either improvement or resolution of dysphagia was achieved in 90% of patients. Treatment delays due to prolonged blood count recovery were common, affecting 66% of patients; most commonly, treatment was delayed in week 3 or 4 of therapy, and less commonly, the treatment cycle was shortened from 4 to 3 weeks.

Another trial in metastatic gastric and gastroesophageal junction cancer was reported by Ajani and colleagues at The University of Texas M. D. Anderson Cancer Center. An overall response rate of 54% among 39 patients was observed.[19] A smaller trial of weekly irinotecan and cisplatin conducted at Memorial Sloan-Kettering Cancer Center (MSKCC) in gastric cancer also demonstrated significant hematologic toxicity, with a response rate of 33% in 18 patients treated.[20] Because of the need to delay therapy when irinotecan and cisplatin are administered weekly for 4 consecutive weeks, a change in the schedule to 2 weeks on and 1 week off has been proposed. A phase II multicenter trial exploring this alternative schedule has recently opened in patients with metastatic esophageal cancer.

### Phase I/II Trials of Irinotecan Combined With Radiotherapy

Numerous studies conducted in cell line and xenograft models have demonstrated the radiation-sensitizing effect of the camptothecins.[21,22] Results of several studies have demonstrated that synergy is greatest when camptothecins are given concurrently with or within a short period of radiation therapy.[23] In one study, the peak sensitization enhancement ratio was reached when radiotherapy was used concurrently with or immediately after camptothecin treatment.[24] The degree of radiosensitization appears to be similar to that of other standard drugs used in combined-modality therapy.[25,26] The mechanism of radiosensitization of the camptothecins is unclear at this time. The radiosensitization effect may be cell-cycle specific; one xenograft study demonstrated a significant increase in the proportion of cells in the G2/M phase, the most radiosensitive phase of the cell cycle after treatment with SN-38.[27] Another trial in cell lines showed an increase in the number of DNA-protein cross links formed, exceeding that expected by the additive damage from radiotherapy and irinotecan, suggesting a synergistic effect.[28] Others have speculated that topoisomerase I inhibitors given shortly after irradiation may cause conversion of single-strand DNA breaks to double-strand breaks, resulting in synergistic lethality to cultured malignant cells.[29]

Few clinical studies have evaluated the combination of irinotecan and radiation therapy. Phase I/II studies of weekly irinotecan and radiation therapy for locally advanced non-small-cell lung cancer have been conducted in Japan; an initial phase I trial established a phase II dose of 45 mg/m² of irinotecan when given once weekly with 6,000 cGy of once-daily fractionated radiotherapy.[30] Dose-limiting toxicities on this trial included esophagitis, pneumonitis, and diarrhea.

A phase II trial conducted in Japan combined 60 mg/m² of once-weekly irinotecan with 6,000 cGy of radiotherapy given in single daily fractions.[31] Observed toxicities included neutropenia, pneumonitis, and esophagitis. Clinical trials in non-small-cell lung cancer, combining radiation therapy and weekly irinotecan with either weekly carboplatin (Paraplatin) or cisplatin, are currently being conducted in the United States at Vanderbilt University in Nashville, and Fox Chase Cancer Center in Philadelphia.

### Phase I Trial of Irinotecan, Cisplatin, and Radiation in Esophageal Cancer

A phase I trial combining concurrent radiation therapy with weekly irinotecan and cisplatin in patients with locally advanced esophageal cancer is near completion at MSKCC. The primary study end point is to establish the maximum tolerated dose of weekly irinotecan that can be combined with weekly cisplatin and concurrent radiotherapy in esophageal cancer. Eligible patients have previously untreated, locally advanced esophageal squamous or adenocarcinoma without evidence of distant metastatic disease. Adequate performance status and organ function are required. Patients are staged with computed tomography (CT) scan and positron emission tomography scan to
evaluate for metastatic disease. All patients undergo local tumor staging with endoscopic ultrasound, and patients with early-stage T1, N0 tumors are excluded. Surgery is not mandated as part of the study, but may be considered after treatment.

The treatment schema for the trial is shown in Figure 1. Dose-limiting toxicity is defined as toxicity that necessitates a 2-week treatment delay during radiotherapy. Induction chemotherapy consists of weekly irinotecan (65 mg/m²) and cisplatin (30 mg/m²), 2 weeks on and 1 week off, for two 3-week cycles. Induction chemotherapy is given primarily to allow for relief of dysphagia prior to beginning the combined chemoradiotherapy. Induction chemotherapy is followed by 6 weeks of radiotherapy, with radiation administered in 180-cGy daily fractions from Monday to Friday to a total dose of 5,040 cGy. During radiation treatment, cisplatin is administered concurrently at a fixed dose of 30 mg/m² followed by escalating doses of irinotecan (40, 50, 65, and 80 mg/m²), once weekly on days 1, 8, 22, and 29 of radiation therapy. The dose level of 80 mg/m² was included given the 2-week-on, 1-week-off chemotherapy schedule during radiation, potentially permitting further irinotecan dose escalation.

Patient demographics are outlined in Table 1. Of 18 patients entered so far, 15 have completed therapy. Therapy has been remarkably well tolerated, with minimal hematologic toxicity noted in treated patients even to a dose level of 65 mg/m² of irinotecan. Median absolute neutrophil and platelet nadirs at each dose level are shown in Table 2. No significant grade 3 or 4 toxicity, including esophagitis or diarrhea, has been observed, with the exception of one patient treated with irinotecan at 50 mg/m² who developed reversible grade 3 pneumonitis (which resolved). At the 80 mg/m² irinotecan dose level, one of three patients completing therapy has had dose-limiting hematologic toxicity (a 2-week delay in radiotherapy due to neutropenia and thrombocytopenia). Three additional patients are currently completing therapy at this dose level.

An unexpected toxicity, which cannot clearly be explained and whose relation to therapy is uncertain, is the observation (in 3 of 15 patients) of asymptomatic pulmonary emboli documented on the posttherapy CT scan of the chest and abdomen. A coincidental deep venous thrombosis was documented in only one of these three patients. In previous phase I/II trials of weekly irinotecan and cisplatin that have included more than 100 patients, no increase in the incidence of thromboembolic events, including deep venous thrombosis or pulmonary embolism, has been observed.[17,18,20,32] Because of this potential complication, the protocol was revised to include daily, low-dose warfarin sodium (Coumadin) prophylaxis during combined chemoradiotherapy.

Thirteen patients are evaluable for response to therapy, of whom 10 have undergone surgery. Five clinical complete responses have been observed (38%). Pathologic complete response was observed in 3 of 10 patients (30%). An additional two patients had only microscopic residual cancer (20%).

**Future Directions**

The preliminary activity and excellent tolerability of weekly irinotecan, cisplatin, and radiation compare favorably with older regimens combining infusional 5-FU and cisplatin with radiotherapy, and more recent trials combining paclitaxel, cisplatin, and radiotherapy. We plan to conduct a formal phase II trial of this regimen of induction chemotherapy followed by chemoradiotherapy, with weekly cisplatin and irinotecan as preoperative therapy, in locally advanced esophageal cancer. Given the minimal toxicity observed, further exploration of other phase I combinations employing this chemoradiotherapy regimen is planned.

Upcoming trials in the phase I setting include addition of weekly paclitaxel (given over 1 hour) to weekly irinotecan, cisplatin, and radiotherapy, as well as the addition of some of the new molecular-targeted therapies. Given the potential role of angiogenesis in tumor growth and metastasis, a planned phase I trial will combine irinotecan, cisplatin, and radiation with the novel antiangiogenic agent SU5416 (Iressa). SU5416 inhibits the tyrosine kinase involved in signal transduction via the angiogenic growth factor receptors flk-1 (fetal liver kinase-1), PDGF (platelet-derived endothelial growth factor), and VEGF (vascular endothelial growth factor).[33]

**References:**


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