**Phase I Study of Irinotecan and Concurrent Radiation Therapy for Upper GI Tumors**

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Irinotecan (Camptosar) is an active chemotherapeutic agent for lung, gastric, esophageal, and colorectal cancers and a potent radiosensitizer. This phase I study was designed to assess the maximum tolerated dose of weekly

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**Introduction**

Although the incidence of gastric carcinoma has declined in the United States over the past 40 years, it remains the eighth leading cause of cancer death. In addition, for reasons that are as yet unclear, the incidence of gastroesophageal and esophageal carcinoma (particularly adenocarcinoma) appears to be increasing.[1] Smoking has recently been implicated, but the evidence appears weak.[2,3] Fifty percent of patients with upper gastrointestinal (GI) malignancies present with unresectable locally advanced or metastatic cancer.[4] A recent approach for the treatment of locally advanced upper GI tumors is multidisciplinary. However, patients with coincidental medical problems, elderly patients, and those with a history of smoking and/or heavy alcohol consumption may not be appropriate candidates for radical surgery. These patients especially will need chemoradiotherapy for their upper GI tract tumors.

Irinotecan (Camptosar) is a plant alkaloid that was isolated from Camptotheca acuminata.[5] Irinotecan has strong anticancer activity in vitro[6] and in various experimental animal cancer models.[7] Because it had demonstrated minimal efficacy in early clinical trials and severe toxicity, this chemotherapeutic agent was not popular in the United States.[8-13] There have been many attempts to synthesize derivatives of camptothecin in order to reinforce its anticancer activity and to decrease its toxicity.[14,15]

The water-soluble derivative of camptothecin, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy camptothecin (irinotecan) has been shown to have high antitumor activity and low toxicity in murine tumors.[7,16] Furthermore, Tsuruo et al have demonstrated that irinotecan is effective against pleiotropic drug-resistant tumors in vitro and in vivo.[17] It appears that camptothecin and irinotecan strongly inhibit mammalian DNA topoisomerase I.[18,19]

A phase I clinical study of irinotecan, in which the drug was given intravenously in a weekly dose, has shown that leukopenia and unpredictable diarrhea are dose-limiting toxicities, and that 100 mg/m² is the maximum tolerated dose (MTD).[20,21] A partial response was observed in patients with advanced non-small-cell lung cancer (NSCLC) who were treated with 100 mg/m² or more of irinotecan in this phase I study.[21]

A recent publication reports the outcome of the investigational use of irinotecan to increase tumor radiosensitivity.[22] Human lung tumor xenografts were treated with either irinotecan 10 mg/kg intraperitoneally on days 1, 5, and 9; single-dose radiation (10 Gy/leg) on day 1; or a combination regimen of both treatments, with radiation given 1 hour after the first dose of irinotecan. DNA flow cytometry studies were performed to define the cell cycle changes following treatment for 1 to 12 hours with 0, 0.5, 2.0, or 8.0 ng/mL SN-38, the major active metabolite of irinotecan. In the small-cell and small-cell/large-cell carcinoma xenografts, combination treatment resulted in significant tumor regression compared with the use of irinotecan or radiation treatment alone.

No severe weight loss or increased skin reaction was observed following the combined treatment.
Flow cytometry studies showed that the proportion of cells in G2/M-phase, the most radiosensitive phase, increased after 1-hour exposure to the lowest dose of SN-38 (0.5 ng/mL). These findings suggest that irinotecan is a potent radiosensitizing agent, and that its activity is related to the cell cycle.[22]

Based on the preclinical data and a few phase I studies indicating irinotecan to be an active chemotherapeutic agent as well as a radiosensitizer for upper GI tumors, we conducted a phase I study to assess the MTD of weekly irinotecan given with concurrent daily continuous radiotherapy for upper GI tumors.

**Patients and Methods**

This phase I study was initiated in January 1998. Patients were eligible after the histology of their tumors was confirmed. They were to have advanced, unresectable gastric, gastroesophageal, or esophageal carcinoma. Patients previously treated by chemotherapy without irinotecan or those with recurrent unresectable tumors were eligible. Patients had to be 18 years of age or older with a performance status of 0, 1, or 2 (Zubrod performance scale) and a life expectancy of at least 12 weeks.

Additional eligibility requirements included a pretreatment granulocyte count >1,500/mL, hemoglobin level ≥ 9 g/dL, a platelet count ≥ 100,000/mL, adequate renal function as documented by serum creatinine ≤ 2.0 mg/dL, and adequate hepatic function as documented by a serum bilirubin level < 1.5 mg/dL regardless of liver involvement secondary to tumor. In addition, serum glutamic-oxaloacetic transaminase (SGOT) had to be ≤ 3 times the institutional upper limit of normal (ULN) unless the liver was invaded with tumor, in which case the SGOT had to be ≤ 5 times the institutional ULN. Patients who had received up to two prior regimens of systemic chemotherapy (excluding irinotecan) were eligible for study entry.

Exclusion criteria included previous treatment with irinotecan or topotecan (Hycamtin), or prior radiation therapy to the thorax or upper abdomen. Also excluded were patients with any active or uncontrolled infection, including known infection with human immunodeficiency virus, patients with psychiatric disorders that would interfere with consent or follow-up, or patients with a history of myocardial infarction within the previous 6 months or congestive heart failure that required therapy. Patients with a history of prior malignancy (except for adequately pretreated basal cell carcinoma, squamous cell skin cancer in situ, or other cancer for which the patient was disease-free for at least 5 years) were also barred from the study.

Baseline measurement of the tumor site and all known metastatic disease had to be documented by computed tomography (CT) scans, x-ray, or other radiographic assessments before treatment could be instituted, and an informed consent form had to be signed by the patient before registration into the study.

**Treatment Plan**

**Chemotherapy**

At least three patients were treated at each irinotecan dose level. Doses were escalated in sequential groups of three patients until the MTD was established or the highest intended dose level was tested. Dose escalation was not allowed for individual patients. All three patients at each dose level were to receive all five doses of irinotecan before the next cohort was started at the next higher dose level. Cohorts could be expanded to six patients as necessary. The starting dose level of irinotecan was 30 mg/m²/wk infused over 90 minutes. All patients were premedicated prior to irinotecan dosing to prevent nausea and vomiting.

The following dose levels were employed: dose level 1, 30 mg/m²; level 2, 40 mg/m²; level 3, 50 mg/m²; level 4, 60 mg/m²; level 5, 70 mg/m².

A weekly dose of irinotecan was given if the granulocyte count was ≥ 1,000/µL, the platelet count...
was \geq 100,000/\mu L, and any other treatment-related toxicities were \leq \text{grade 1}.

**Radiotherapy**

The treatment plan for radiation therapy was to give a total tumor dose of 45-50.4 Gy in 1.8 Gy fractions for a total of 25-28 fractions, delivered over 5 weeks. The dose was calculated at the midplane. All patients were reassessed at 4 weeks after completion of chemoradiation therapy. Irinotecan was administered 1 hour prior to administration of radiation therapy on day 1 of each week of 5 treatment weeks.

The linear accelerator generated 6 MV or 18 MV photons. The minimum target skin distance was 80 cm. Field placements were anterior-posterior/posterior-anterior and anterior with two posterior obliques to avoid high dosing to the heart. The two sharp posterior angles were used to minimize the volume of the lung included within the irradiated fields. Target volume was based on the size of individual tumors. The 2-cm lateral margin and 3-cm margin along the vertical axis of the target mass were used.

Radiation therapy was withheld on any planned treatment day on which the patients exhibited grade 3 toxicity. A toxicity that delayed planned radiation therapy for more than 2 weeks was considered dose-limiting for the purpose of this study.

All patients were seen weekly in the Radiation Oncology Department and every 2 weeks in the GI Center during chemoradiation therapy.

**Results**

There were 18 patients enrolled in this study between January and November 1998. All patients were evaluable for toxicities and 12 for response. Male to female ratio was 16:2; ages ranged from 30 to 76 years with a median of 59 years. Of these, 6 patients had esophageal malignancies, 9 had lesions in the gastroesophageal junction, and 3 had cancer of the stomach. Tumor pathology included 1 squamous, 14 adenocarcinoma (1 well differentiated, 9 moderately differentiated, and 4 poorly differentiated), and 3 signet ring carcinomas. In all, 12 patients had T3 and 6 had T4 lesions; 6 patients had N0 disease and 12 had N1 disease.

Dose levels of irinotecan were as follows: three patients received 30 mg/m$^2$, three patients received 40 mg/m$^2$, four patients received 50 mg/m$^2$, and six patients received 60 mg/m$^2$, one patient received 70 mg/m$^2$. Radiation doses ranged from 30 Gy to 50.4 Gy.

There were 4 patients who received 50.4 Gy in 28 fractions, 12 received 45 Gy in 25 fractions, 1 patient received 27 Gy in 15 fractions, and another received 34 Gy in 19 fractions.

Major toxicities (grade 3/4) were hematologic. Three patients developed neutropenia, including one patient with neutropenic fever, one patient had sepsis, and one patient developed chills. Two patients hemorrhaged, and two had severe anemia. Patients with grade 3/4 GI toxicities included two with nausea, four with vomiting, three with dehydration, three with anorexia, and one with constipation. No patient experienced severe pneumonitis.

Of 12 evaluable patients, 7 (58%) had a response, including 2 complete responses; 4 patients (30%) had no change. Only 1 patient had progressive disease. Median time to progression was 27.5 weeks. Survival ranged from 1 to 15 months; median survival was 8 months.

**Discussion**

Among the camptothecins, irinotecan appears active as a single agent in patients with advanced gastric carcinoma.[23] Irinotecan plus cisplatin (Platinol) was also reported to have a response rate of 42%.[24]

Camptothecin is an alkaloid obtained from plants such as the *Camptotheca acuminata* tree. The
original clinical preparation, camptothecin sodium, was evaluated in clinical trials in the late 1960s and early 1970s, but was abandoned due to severe and unpredictable hemorrhagic cystitis.[25-27] Irinotecan is a semisynthetic derivative of camptothecin that possesses greater aqueous solubility, greater in vitro and in vivo activity, and is associated with less severe and more predictable toxicity than camptothecin.[28-30]

Both camptothecin and irinotecan are potent inhibitors of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription. The enzyme normally functions during DNA replication causing transient breaks in a single strand of DNA that release the torsional strain caused by synthesis of a new strand of DNA or RNA around a double helix. The camptothecins target this topoisomerase I-DNA complex, stabilize it, and then inhibit reannealing of the parent DNA. When an advancing replication fork collides with the camptothecin-topoisomerase I-DNA complex, double-stranded DNA breaks occur that lead to cell death.[31,32] Preclinical studies in human lung tumor xenografts have shown that irinotecan is a potent radiosensitizing agent, and that its activity is related to the cell cycle.[22]

Preliminary, preclinical, and clinical studies demonstrate a synergistic effect of irinotecan and radiation and further substantiate the radiosensitizing activity of irinotecan. Interaction with cellular processes such as DNA replication, RNA transcription, and DNA repair may transform potentially sublethal DNA damage into sublethal DNA damage. It is plausible that such sublethal DNA damage could then be converted into lethal DNA damage with the addition of radiation-induced DNA damage.[22]

A phase I/II study of weekly irinotecan given concurrently with radiation in patients with locally advanced NSCLC demonstrated response and manageable toxicities. Doses of irinotecan started at 30 mg/m$^2$ and were escalated to 45 and 60 mg/m/week. In 26 eligible patients, the dose-limiting toxicities were esophagitis, pneumonitis, and diarrhea. The MTD was estimated to be 60 mg/m and the recommended dose for a phase II study was 45 mg/m. In this phase II study, 2 of 24 evaluable patients achieved a complete response and 16 attained a partial response, resulting in an overall response rate of 76%.

The investigators concluded that a combination of concurrent weekly irinotecan and radiotherapy is feasible and active for locally advanced NSCLC.[33] These results were extended in a phase II trial in previously untreated patients with stage IIIA/B NSCLC where 24 eligible patients received irinotecan 60 mg/m weekly and a total of 60 Gy chest radiation therapy. The response rate was 79%, with pneumonitis and esophagitis being the principle toxicities.[33]

Administering up to 60 mg/m irinotecan with concurrent radiation therapy of 45 Gy over 5 weeks has been shown to be a feasible approach in previously treated patients.

In the future, cell proliferation rates must be considered when providing accelerated radiation therapy or conventional radiation therapy in combination with radiosensitizing agents. Combined treatment with more efficacious systemic agents and more aggressive locoregional treatments to produce 5-year survival rates better than 25% with less than 10% treatment-related mortality is warranted. The combination of irinotecan and concurrent radiotherapy can be given safely for esophageal and gastric cancers. It should also be investigated for the treatment of lung and other cancers.

References:


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