Irinotecan in Preoperative Combined-Modality Therapy for Locally Advanced Rectal Cancer

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Irinotecan (CPT-11, Camptosar) is a semisynthetic water-soluble derivative of the plant alkaloid camptothecin. This review will focus on the potential use of irinotecan in combination with fluorouracil (5-FU) in the preoperative combined-modality treatment of advanced rectal cancer.

**Introduction**

Since irinotecan (CPT-11, Camptosar) was approved by the US Food and Drug Administration for use in fluorouracil (5-FU)-refractory advanced colorectal cancer, based on its demonstrated antitumor activity,[1] studies have reported the utility of irinotecan in first-line treatment of colorectal cancer.[2-9] In April 2000, irinotecan was approved by the Food and Drug Administration for use as a component of first-line therapy in combination with 5-FU and leucovorin for metastatic colorectal cancer. Additionally, preclinical and clinical studies have suggested the potential effectiveness of irinotecan as a radiosensitizing agent.[10-16]

Combined-modality treatment with chemotherapy and radiation can improve the therapeutic index in rectal carcinoma.[17] Fluorouracil is the most widely used chemotherapeutic agent in the clinical management of patients with rectal cancer. The benefits of combining fluoropyrimidines and radiation are thought to be due to radiosensitization.[18-20] Although postoperative irradiation with systemic chemotherapy is currently considered to be the most effective treatment in the adjuvant setting,[21-23] preoperative irradiation has demonstrated distinct advantages in the treatment of this disease.[24] These include the decrease of tumor seeding while the numbers of oxygenated cells during surgery are increased, and the elimination of postsurgical small bowel fixation in the pelvis. In addition, preoperative radiation therapy allows the surgeon to perform sphincter-sparing, low anterior resection.[25-37] Results of randomized trials also indicate that preoperative irradiation is more effective than postoperative in reducing local failure.[38-40]

**Fluoropyrimidine Cytotoxicity**

Fluorouracil is an analog of uracil and is metabolized to form several nucleotides including fluorodeoxyxuridine monophosphate (F-dUMP). This nucleotide inhibits the enzyme thymidylate synthase, thus interfering with the synthesis of new strands of DNA.[41,42] F-dUMP with a folate cofactor binds to thymidylate synthase, leading to depletion of the product deoxythymidine monophosphate (dTMP) and, ultimately, of deoxythymidine triphosphate (dTTP). This results in accumulation of the substrate dUMP and deoxyuridine triphosphate (dUTP), so that dUTP is misincorporated into DNA. Prolonged thymidylate synthase inhibition depletes dTTP pools, leading to inhibition of DNA synthesis, DNA fragmentation, G1/S cell-cycle arrest, and ultimately, cell death. Fluorouracil is also incorporated into RNA and DNA, but the inhibition of thymidylate synthase is considered to be its main mechanism of action and ultimately responsible for the DNA-directed effects of the drug.[43]

**Fluoropyrimidine Radiation Interactions**

Radiosensitization is related to thymidylate synthase inhibition and is accompanied by both a decrease in double-stranded breaks[44-46] and sublethal damage repair.[47-49] Fluorouracil radiosensitization is enhanced by leucovorin, presumably by potentiation of thymidylate synthase inhibition.[17,46,48]

Various mechanisms have been proposed to account for fluoropyrimidine-mediated sensitization.
These include (1) alteration of nucleotide pools, (2) redistribution of cells to a relatively radiosensitive phase of the cell cycle, and (3) incorporation of fluorodeoxyuridine triphosphate into DNA.[17]

Although each of the proposed mechanisms may play a role in fluoropyrimidine-mediated sensitization, some studies suggest that cytotoxicity may be inconsistent with radiosensitization.[19] The inappropriate progression of cells through the G1/S boundary and into S phase during fluoropyrimidine exposure has also been proposed as a mechanism of radiosensitization.[50]

**Radiation Sensitization With Irinotecan**

Preclinical studies have demonstrated synergistic effects and have suggested radiosensitizing activity when the topoisomerase I inhibitor irinotecan is combined with radiation. Irinotecan may potentiate the lethal effects of ionizing radiation by attaching to the DNA-topoisomerase adducts in sites of DNA single-strand breaks. Subsequently, the irinotecan-topoisomerase I-DNA complexes interact with advancing replication forks during the S phase of the cell cycle, converting single-strand breaks into irreversible DNA double-strand breaks, resulting in cell death.

Fractionated irradiation synchronizes and resorbs the tumor cell population, leaving the majority of the cells in the S phase of the cell cycle and thus more sensitive to irinotecan.[51] With potentiating effects more pronounced for chromosome aberrations of the exchange type, it has been suggested that the interaction of unrepaired radiation- and camptothecin-induced lesions during replication may be involved in the observed drug-radiation synergism.[11]

Further studies have demonstrated radiation sensitization with irinotecan in human tumor xenografts. Significant tumor regression was shown when irinotecan was administered 1 hour prior to a single dose of irradiation compared with the response to radiation therapy alone.[10] Other studies have also demonstrated sensitization when the drug is given following irradiation.[14]

**Irinotecan in Combined-Modality Therapy**

In a clinical phase I/II trial in which weekly irinotecan was given with concurrent irradiation of 60 Gy administered in 30 fractions over 6 weeks to patients with non-small-cell lung cancer, the maximum tolerated dose of irinotecan was 60 mg/m².[15] A total of 24 previously untreated patients with unresectable stage IIIA or IIIB non-small-cell lung cancer received chemoradiation with irinotecan given at a dose of 45 mg/m². The six planned courses of irinotecan were delivered to 71% of patients; five courses were administered to 21% of patients. External beam irradiation was completed in 88% of patients, with treatment delays in three patients because of fever or fatigue. The overall objective response rate was 76%, with two patients achieving a complete response and 16 a partial response. Dose-limiting toxicities were esophagitis, pneumonitis, and diarrhea. The conclusion of this study was that combined-modality therapy with irinotecan is feasible and active in the treatment of locally advanced non-small-cell lung cancer.

In a study by Minsky and colleagues at Memorial Sloan-Kettering Cancer Center, a divided dose bolus schedule of escalating doses of irinotecan (Monday through Friday) was administered on weeks 1, 2, 4, and 5 during a standard 6-week radiation therapy cycle (50.4 Gy) for preoperative treatment of locally advanced unresectable rectal cancer. The maximum tolerated dose was 10 mg/m²/d. Because complete responses were fewer than anticipated, this regimen was abandoned.[52]

How then might irinotecan be more effectively incorporated into a combined-modality regimen in the treatment of rectal cancer? Our group at the Kimmel Cancer Center of Thomas Jefferson University is currently conducting a phase I study with protracted continuous infusion of 5-FU given with weekly irinotecan after 4 consecutive weeks and concurrent external beam irradiation (total of 45.0 Gy in 1.8-Gy fractions) given daily. The objective was to determine the maximum tolerated dose of weekly irinotecan combined with 5-FU and concomitant irradiation given preoperatively in previously untreated patients with primary or recurrent clinical stage T3/T4 adenocarcinoma of the rectum.

The treatment regimen was as follows: escalating doses of irinotecan at 30 to 50 mg/m² over 90
minutes on days 1, 8, 15, and 22. Fluorouracil was given as a protracted venous infusion at 300 mg/m²/day initially and subsequently reduced to 225 mg/m² on days 1 through 5 weekly during radiation therapy. Surgery was performed 8 to 10 weeks following completion of therapy. At the time of this preliminary report, a total of 38 patients were enrolled in the study. One patient was removed from the study for noncompliance and one due to early surgical intervention. All are evaluable for toxicity. The incidence of grade 3/4 toxicities at each dose level is outlined in Table 1.

Hematologic toxicities were mild. The major dose-limiting toxicities were diarrhea, intravenous catheter infections, and thrombi. Of 34 patients who have undergone surgery, 10 complete pathologic remissions and 6 patients with minimal residual disease were observed; 4 patients are awaiting surgery. The conclusion was that the combination of irinotecan, 5-FU, and concomitant radiation therapy given preoperatively in this patient population was well tolerated. The maximum tolerated dose had not been achieved in this ongoing investigation.[53]

**Conclusion**

The radiosensitizing properties of 5-FU have been well delineated. Clinical studies evaluating the potential of irinotecan are underway. Preclinical evidence from a murine model suggests effectiveness. The ability to administer full doses of irinotecan and 5-FU allows the potential of double radio enhancement. Further studies will determine the effectiveness of this combination in the management of patients with adenocarcinoma of the rectum.

**References:**


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