Irinotecan and Radiation in Combined-Modality Therapy for Solid Tumors

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Irinotecan (CPT-11, Camptosar) is a camptothecin derivative that is thought to exert its cytotoxic effects by targeting topoisomerase

**Introduction**

Solid tumors account for the majority of all malignancies and are responsible for a large proportion of deaths in the industrialized world. In the United States in the year 2001, 1,268,000 new cases of invasive cancer will be diagnosed and 553,400 Americans are expected to die from their cancers.[1] While currently about half of all patients are cured, the other 50% will die of their disease.[1] Current treatments are based on one of three modalities: surgery, radiation, or chemotherapy. Surgical treatments often fail because either the tumor recurs in the tumor bed, since an insufficient margin of normal tissue was removed in order to preserve function and cosmesis, or distant metastases develop. Radiation treatments fail because distant metastatic disease develops or the dose required to sterilize the tumor is limited by the surrounding normal tissues, and the tumor recurs locally. Chemotherapy tends to have less of a curative effect on gross disease but may be able to decrease the risk of distant relapse when administered in an adjuvant setting.

More traditional treatments like cisplatin (Platinol) and doxorubicin are now being joined by a new generation of drugs active against a broad range of solid tumors. These new agents—including paclitaxel (Taxol), docetaxel (Taxotere), gemcitabine (Gemzar), vinorelbine (Navelbine), irinotecan (CPT-11, Camptosar), and others—are associated with promising response rates of 20% to 50% in the setting of metastatic disease.[2] It is hoped that these agents may improve outcomes in patients with earlier-stage disease as well.

**Multiple Treatment Modalities**

Modern clinical trials are focusing more on integrating multiple treatment modalities to maximize outcomes. Steele and Peckham outlined several mechanisms for the possible interaction of radiation and chemotherapies: spatial cooperation, enhancement of tumor response, radioprotection, and nonoverlapping toxicities (or toxicity independence).[3] Spatial cooperation describes a situation in which disease located in a specific anatomic site is missed by one agent but treated by another. Enhancement occurs when the administration of one agent increases the effect of another agent, or when the effect of the combination is greater than would be expected with either agent alone. Radioprotection refers to administration of a chemotherapeutic agent that allows for safe delivery of increased radiation.

Ample literature exists on the ability of different drugs to enhance radiation effect when the two modalities are delivered concurrently. This article will provide an overview of concurrent administration of irinotecan and radiation to patients with solid tumors, with a focus on irinotecan’s mechanism of action, its radiosensitizing effects, and current clinical trials evaluating concurrent irinotecan and radiation.

**Camptothecins**

**Background and Mechanism of Activity**

Irinotecan is a member of a relatively new group of anticancer agents, the camptothecins, whose activity is believed to be achieved by targeting DNA topoisomerase I.[4-7] The human DNA
topoisomerase I is a monomeric 100-kDa protein that relaxes supercoiled DNA by introducing a single-strand break in DNA, followed by the passing of the intact strand through the break prior to re-ligation.[4-9] This activity is key in many aspects of DNA metabolism, including transcription, replication, and regulation of DNA supercoiling, which is important in maintaining genomic stability. It is believed that the camptothecins function by stabilizing a topoisomerase I-DNA intermediate, called the cleavable complex, such that the 5′ phosphoryl end of the DNA single-strand break is bound covalently to a topoisomerase I tyrosine residue.[10] It is believed that collision of this drug-trapped complex with the DNA replication machinery will lead to G2 phase cell-cycle arrest and cell death.[10]

Camptothecin, the parent compound, was initially isolated from the tree *Camptotheca acuminata* and found to have a broad spectrum of activity in a variety of solid tumors.[11] However, early clinical trials with the ring-open form of the drug showed excessive toxicity and the trials were terminated.[12] More recently, interest has been rekindled in these drugs with the advent of derivatives that have significant antitumor activity and much less toxicity. Irinotecan, one of these derivatives, is actually a prodrug that is metabolized intracellularly into SN-38.[13] SN-38 is approximately 1,000 times more potent than irinotecan in inhibiting topoisomerase I.[14] All of the camptothecins have a terminal lactone ring that can be hydrolyzed to a less active carboxylate species. Under acidic conditions, however, like those expected in the tumor microenvironment, the active lactone species is favored.[13]

The plasma half-life of SN-38 by intravenous infusion is 5.9 to 13.8 hours,[13] and this may have implications in terms of both direct cytotoxicity and radiosensitization. SN-38 is eliminated primarily through hepatic glucuronidation and it is thought that a decreased ability to glucuronidate the drug correlates with increased gastrointestinal side effects.[13] One of the major side effects of irinotecan is late-onset diarrhea, which is possibly related to the high S-phase fraction of the intestinal mucosa as well as action of intestinal flora glucuronidase in cleaving the camptothecin-glucuronidase conjugate, leading to the drug's release into the intestinal lumen.[15] Other common toxicities include neutropenia, nausea, vomiting, anorexia, fatigue, asthenia, and elevation of hepatic transaminase levels.[13]

Several other camptothecin derivatives have been shown to have significant cytotoxic effects and are at varying stages of development. These include topotecan (Hycamtin),[16,17] 9-aminocamptothecin (9 A-C),[18] and 9-nitrocamptothecin (RFS-2000).[19] Of these, topotecan has undergone the most extensive clinical testing; it is indicated for treatment of patients with platinum-resistant ovarian cancer and small-cell lung cancer after failure of first-line therapy.[16]

**Irinotecan Activity**

Response rates with irinotecan have ranged from 18% to 32% in metastatic colorectal cancer,[20,21] 15% to 32% in non-small-cell lung cancer,[22,23] and 10% to 47% in small-cell lung cancer.[24,25] It is also active in other malignancies, including cervical, gastric, ovarian, and central nervous system tumors.[13] While its activity in advanced disease is promising, convincing evidence now indicates that the camptothecins, including irinotecan, have significant radiosensitizing properties.[10,17] This discovery may potentially lead to improved local control of solid tumors when irinotecan is used concurrently with radiation. In the setting of localized and potentially curable disease, it is hoped that this enhanced activity will translate into improved survival.

Several hypotheses exist regarding the mechanism of interaction between radiation and irinotecan, each with varying amounts of supportive evidence. One hypothesis suggests that inhibition of topoisomerase I by camptothecin or its derivatives leads to inhibition of repair of radiation-induced DNA strand breaks.[18,26,27] A second hypothesis suggests that camptothecin or its analogs causes redistribution of cells into the more radiosensitive G2 phase of the cell cycle.[28] Another hypothesis is that topoisomerase I-DNA adducts are trapped by irinotecan at the sites of radiation-induced single strand breaks, leading to their conversion into double-strand breaks.[29-31] In essence, the drug-stabilized cleavable complex, with a concealed single-strand DNA break, may potentially act as a point of sublethal DNA damage. Interaction with cellular processes like
transcription and DNA repair may act to turn this "potentially sublethal damage" into "sublethal damage." It is possible that the addition of radiation may in turn change this "sublethal damage" into "lethal damage."[10] It is also suggested that high levels of topoisomerase I are associated with high levels of cleavable complex formation.[32] These high enzyme levels have been documented in several tumor specimens,[33] suggesting that irinotecan use may be beneficial in improving the therapeutic ratio vis-à-vis normal tissue effects.

Johnson and McNerney initially reported in 1985 that topoisomerase I activity increased by about 300-fold after irradiation of human peripheral blood lymphocytes or cultured lymphoblastoid cells.[34] Other investigators have not found any increase in activity.[34] This variance could be related to the cell population or to the genomic location of the topoisomerase pool under examination. The predominance of the particular mechanism involved in radiosensitization may depend on which camptothecin derivative is used; now, there is insufficient evidence to identify the underlying mechanism with certainty.

Irinotecan Radiosensitization

Chen et al showed that camptothecin derivatives radiosensitized log-phased human MCF-7 breast cancer cells in a schedule-dependent manner.[35] Essentially, cells that were exposed to 20(S)-10,11 methylene dioxy camptothecin before or during radiation showed sensitization ratios of 1.6, while those treated with the drug after radiation had substantially less enhancement of radiation-induced DNA damage. These results suggest that patients should receive the drug shortly before or during radiation to reap the full radiosensitization potential of combination treatment. Other investigators found similar results: in one study, for example, the major increase in radiosensitization in human malignant melanoma (U1-Mel) cells treated with 9-aminocamptothecin occurred in the first hour after irradiation.[36]

Amorino et al examined the interaction between radiation and 9-nitro-20(S)-camptothecin (9-NC), which is an orally active camptothecin derivative.[19] Results showed a concentration-dependent dose-enhancement ratio of up to 2.0 in the human lung cancer cell line H460. They also found that 9-NC partially inhibited split-dose recovery in the same cell line, suggesting inhibition of sublethal damage recovery. Furthermore, interesting early data show that SN-38 sensitized proliferating WHO3 cells (a human esophageal cancer cell line) to radiation under hypoxic conditions.[37]

Other evidence of the radiosensitizing abilities of camptothecins comes from more complex model systems. Omura et al examined radiosensitization with SN-38 in HT-29 spheroids derived from a human colon cancer cell line.[27] Cell kill was significantly enhanced when radiation was combined with irinotecan. The largest gains in cytotoxicity occurred when irinotecan was given just before or just after the radiation. Results also suggested that the mechanism of radiosensitization in the spheroids is through inhibition of potentially lethal damage repair. Evidence from human small-cell and mixed small- and large-cell lung cancer xenografts also indicates that significant radiosensitization occurs with the combination of irinotecan and radiation. According to flow cytometry, the proportion of cells in the G2/M phase increases 1 hour after treatment with SN-38, suggesting that some of the radiosensitization occurs through cell-cycle-related mechanisms.[28]

Clinical Trials

The large volume of in vitro and in vivo evidence of irinotecan’s radiosensitizing abilities has led to clinical trials. It is hoped that irinotecan would improve the therapeutic ratio by selectively targeting tumor cells, which tend to be more acidic and which may have higher topoisomerase levels. Clinical trials in this area have begun and early reports of response rates are encouraging.

Non-Small-Cell Lung Cancer

The majority of clinical studies of irinotecan combined with radiation have involved patients with non-small-cell lung cancer. Important results from large multicenter trials suggested that concurrent chemotherapy and radiation is a reasonable treatment strategy to potentially improve outcome with acceptable side effects.[38-40]
Takeda and colleagues examined weekly irinotecan at escalating doses with concurrent thoracic radiation (60 Gy in 30 fractions over 6 weeks) in a phase I/II trial.[41] Patients with stage III non-small-cell lung cancer and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 received irinotecan at the initial dose of 30 mg/m² IV weekly for 6 weeks, with the dose escalated in 15-mg/m² increments in successive cohorts. Five patients received the maximum tolerated dose of 60 mg/m², two of whom had World Health Organization (WHO) grade 3/4 esophagitis and three, grade 3/4 pneumonitis. An additional 10 patients treated in the phase II portion of the trial received irinotecan at 45 mg/m², for a total of 17 patients treated at this dose level. Toxicities in the phase II portion included one case of fatal pneumonitis and one case of grade 3 diarrhea. The overall response rate was 76.9%; the 1-year survival rate was 61.5% at 22 months of follow-up.

Saka and colleagues performed a phase II trial in which patients with locally advanced non-small-cell lung cancer received irinotecan at 60 mg/m² IV weekly with concurrent thoracic radiation (60 Gy).[42] Among all 24 patients, 71% completed the planned chemotherapy and 88% completed the planned radiotherapy. Partial responses were seen in 79% of patients. Toxicities included three cases of grade 3 pneumonitis, two cases of grade 3 esophagitis, two cases of grade 3 neutropenia, and one case of grade 3 fever. No grade 4 toxicities were observed. The investigators concluded that this was a tolerable and active regimen for patients with non-small-cell lung cancer.

Evaluation of irinotecan plus concurrent thoracic irradiation has expanded to include platinum compounds based on their established activity in non-small-cell lung cancer, their radiosensitizing effects, as well as preclinical data.[43] Yokoyama and colleagues in the Japan Clinical Oncology Group conducted a phase I trial in which 12 patients received escalating doses of irinotecan and cisplatin with 60 Gy of concurrent thoracic radiation.[44] Six patients received the level 1 doses of 60 mg/m² (cisplatin) and 40 mg/m² (irinotecan) with the radiation. The chemotherapy was discontinued, however, in two patients before the three planned cycles were completed because of toxicity. At dose level 2 (60 mg/m² of cisplatin and 60 mg/m² of irinotecan), only three patients received all three chemotherapy cycles. The three patients who did not complete chemotherapy also did not complete radiotherapy, in contrast to dose level 1 where all patients completed their planned radiation treatment. Due to the low-dose intensity of irinotecan in dose levels 1 and 2 (irinotecan was often omitted on days 8 and 15 because of leukopenia or diarrhea), the low completion rate for radiation therapy, and the high rate of toxicities (including one death), the study was closed at dose level 2. Although the overall response rate was 67% (8/12 partial responses), overall survival at 1 year was only 33%. An ongoing phase I study being conducted at the Fox Chase Cancer Center may provide further insight into the tolerability of concurrent irinotecan, cisplatin, and thoracic radiation.[45]

Three other Japanese trials of concurrent platinum drugs, irinotecan, and radiation in non-small-cell lung cancer have been reported. In a study by Fukuda et al, 24 patients received two courses of chemotherapy with split-course radiation (irinotecan at 60 mg/m² days 1, 8, and 15 and cisplatin at 80 mg/m² on day 1 were the recommended doses for phase II study).[46] The overall response rate was 65% with some cases of neutropenia, thrombocytopenia, and esophagitis. A follow-up study by the Japanese Lung Cancer Group involved induction cisplatin and irinotecan for two cycles followed by concurrent weekly irinotecan and thoracic radiation.[47] Among 68 enrolled patients, neutropenia (6% incidence of grade 4), esophagitis (4%, grade 3), and pneumonitis (2%, grade 4) were the significant toxicities. The response rate was 63.3% and the estimated 1-year survival was 71.7%. They concluded that induction chemotherapy followed by concurrent thoracic radiation and irinotecan was a promising strategy that merited evaluation in randomized trials.

Finally, a trial assessed combining 60 Gy of thoracic radiation with carboplatin (Paraplatin) and irinotecan.[48] Thirty enrolled patients received carboplatin at 20 mg/m²/d × 5 and irinotecan at a starting dose of 30 mg/m² IV weekly. Both drugs were given weekly for 4 weeks. The irinotecan dose was escalated in 10-mg/m² increments. The maximum tolerated dose of irinotecan was 60 mg/m²; dose-limiting toxicities included pneumonitis, esophagitis, neutropenia, and thrombocytopenia. Three patients had complete responses and 15 had partial responses, for an overall response rate of 60%. Median survival has not been reached, and the 2-year survival is encouraging at 51.3%.

Outside of Japan, there has been one reported trial of irinotecan plus carboplatin and concurrent...
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For the first 18 patients treated on this trial at the Vanderbilt Cancer Center, the response rate has been 61%, and nausea, vomiting, and esophagitis have been the major toxicities (Table 1).[49] While one patient at the first dose level developed grade 5 esophagitis, a further six patients in the expanded cohort did not develop this problem. The maximum tolerated dose of concurrent chest radiation and irinotecan was found to be 40 mg/m²/wk for 6 weeks.

Small-Cell Lung Cancer

The combination of cisplatin and irinotecan has been found to have significant activity in refractory disease,[50] as well as in de novo disease.[52] Data recently presented by the Japanese Clinical Oncology Group showed that four cycles of cisplatin/irinotecan every 4 weeks in extensive-stage small-cell lung cancer significantly increased 1-year survival to 60% (from 40% with standard cisplatin/etoposide therapy).[53] It follows that this combination might improve cure rates if combined with thoracic radiation in limited-stage disease. So far, there is a report of a phase I trial in which patients received cisplatin on day 1 and irinotecan on days 1, 8, and 15 for four 28-day cycles.

 Patients also received 20 Gy of radiation to the chest with each of the first three cycles (total dose: 60 Gy). Of 16 evaluable patients, 4 had a complete response, 11 partial response, and 1 stable disease, for an overall response rate of 94%. The recommended schedule was 40 mg/m² of irinotecan and 60 mg/m² of cisplatin, because at higher doses the limiting toxicity was fatigue.

Further follow-up of these patients and assessment of this combination in a phase II study are warranted.

Head and Neck Cancer

Concurrent chemotherapy and radiation have been shown to be beneficial for head and neck cancer patients when agents with radiosensitizing properties, such as fluorouracil (5-FU), cisplatin, mitomycin (Mutamycin), or hydroxyurea (Hydrea), were included in the regimen. Koukourakis and colleagues published results of a phase I trial of combination docetaxel and irinotecan with radiation for locally advanced squamous cell carcinoma of the head and neck.[54] The planned radiation dose of 66 to 70 Gy was delivered in 6.5 to 7 weeks in combination with chemotherapy. The docetaxel starting dose was 20 mg/m²/wk with planned increases of 5 mg/m² every eight patients (two cohorts) for a total of seven doses. The irinotecan starting dose was 25 mg/m²/wk for 7 weeks and was increased by 15 mg/m² every four patients until dose-limiting toxicities occurred.

All four patients at the third dose level (docetaxel at 25 mg/m²/wk and irinotecan at 55 mg/m²/wk) developed grade 3/4 mucositis requiring > 7-day treatment delays. This delay may partially explain why the lowest complete response rate was seen in patients at this dose level. At the first and second dose levels, grade 2 mucositis was experienced by 7 of 8 patients (the other patient had grade 3 mucositis), and grade 2 asthenia and anorexia occurred in at least half the patients. Interestingly, 9 of 12 patients had documented complete responses based on the post-treatment computed tomography (CT) scans, and three had partial responses. The investigators recommended that the maximum tolerated doses for weekly docetaxel and irinotecan should be 20 and 40 mg/m², respectively, during standard radiotherapy for head and neck cancer.

Another phase I trial examined combining irinotecan with an established regimen of twice-daily radiation, 5-FU, and hydroxyurea.[55] Irinotecan was administered IV daily on days 1 to 5 every 2 weeks for 4 to 5 cycles. Irinotecan was given prior to the radiation at a starting dose of 5 mg/m²/d and was escalated to a maximum dose of 15 mg/m²/d. Of 16 patients entered in the trial, 14 were evaluable for toxicity; 10 developed grade 3/4 mucositis and 8 developed grade 3/4 dermatitis by the third to fifth cycle. Of 8 patients evaluable for response, 6 had either a partial or complete response. The authors concluded that the dose-limiting radiosensitizing contribution of irinotecan was seen at 15 mg/m². Additional patients are being treated in a phase II fashion with irinotecan at 10 mg/m²/d.

Both of these trials show that irinotecan in combination with concurrent radiation and other agents, ie, docetaxel, or 5-FU and hydroxyurea, yields high response rates in locally advanced disease. Dose escalation of irinotecan is limited by mucositis as would be expected with radiosensitization. Further study of irinotecan with concurrent radiotherapy is needed, possibly with incorporation of a mucosal...
protection agent like amifostine (Ethyol)\[56,57\] to help ameliorate toxicities.

**Gastrointestinal Cancer**

The role of chemoradiotherapy in locally advanced gastrointestinal cancer—which often carries a grim prognosis—is worthy of study. Certainly, the activity of irinotecan in metastatic colorectal cancers is encouraging.\[58\] An ongoing phase I trial at the M. D. Anderson Cancer Center is examining the role of escalating weekly doses of irinotecan with concurrent radiation to a total dose of 45 to 50.4 Gy in locally advanced upper gastrointestinal cancers.\[59\] The irinotecan starting dose was 10 mg/m\(^2\)/wk and has been escalated to 70 mg/m\(^2\)/wk without yet reaching the maximum tolerated dose. Median time to progression has been 27.5 weeks in 18 patients. Only 8% of the planned irinotecan doses have been withheld due to side effects.

Another ongoing phase I trial at the Memorial Sloan-Kettering Cancer Center has the following major objectives: determine the dose-limiting toxicity of irinotecan when given weekly with cisplatin and concurrent radiotherapy in patients with locally advanced carcinoma of the esophagus or gastroesophageal junction; determine the maximum tolerated dose and the recommended phase II dose of irinotecan in this regimen; and evaluate the complete response rate after one course of induction chemotherapy followed by concurrent chemotherapy and radiotherapy.\[60\] Patients receive cisplatin induction chemotherapy followed by irinotecan on days 1, 8, 15, and 22. After 2 weeks of rest, patients begin chemoradiation with cisplatin and irinotecan as above on days 1, 8, 22, and 29, and radiotherapy once daily 5 days a week for 5 to 6 weeks. It is hoped that the results of these studies will provide a reasonable basis for future phase II trials.

**Cervical Cancer**

Carcinoma of the cervix is another tumor for which irinotecan has the potential to improve local control. Several randomized trials have shown the benefit of concurrent cisplatin-based chemotherapy and radiation in increasing tumor control and overall survival in this disease.\[61-64\] It is logical to add irinotecan to current protocols based on its radiosensitizing effects, its nonoverlapping toxicities with cisplatin, and impressive response rates of the combination of irinotecan, cisplatin, and radiation in other disease sites.\[2,17\]

In a study by the European Organization for the Research and Treatment of Cancer (EORTC), patients with histologically confirmed, inoperable, progressive, metastatic, or recurrent squamous cell carcinoma of the cervix with no radiation in the preceding 3 months were treated with irinotecan.\[65\] Results showed a 23.5% response rate in a patient population with one or more lesions in an unirradiated area. The response rate was lower in the previously irradiated areas. These results are similar to those from a phase II trial conducted by the Gynecologic Oncology Group.\[66\]

Sugiyama et al also incorporated irinotecan into a regimen for advanced or recurrent disease.\[67\] They treated 29 patients with cisplatin at 60 mg/m\(^2\) on day 1 every 4 weeks and irinotecan at 60 mg/m\(^2\) on days 1, 8, and 15. The response rate was 59% (complete response in two patients), with major toxicities of neutropenia, anemia, nausea/vomiting, and diarrhea. The fact that these advanced-disease patients (some of whom had received up-front radiation therapy) responded significantly to chemotherapy alone makes it appealing to try the addition of irinotecan to concurrent radiation and cisplatin regimens in localized disease.

**Conclusions**

In early studies, radiation has been combined with irinotecan-based chemotherapy for several solid tumor types. This approach seems logical, given data indicating that irinotecan acts as a radiosensitizer. Emerging clinical data from phase I and II trials in non-small-cell lung cancer show response rates of at least 60% and promising 1-year survival rates. Toxicity assessments from these early trials have also demonstrated that these regimens are feasible and tolerable for most patients. Concurrent irinotecan-incorporating chemotherapy regimens may soon be tested in randomized phase II or III trials in patients with non-small-cell lung cancer. Similar promising results with irinotecan-based concurrent chemoradiotherapy regimens have also been seen in trials of head and
neck cancer patients. Given the activity of irinotecan in other tumors, including gastrointestinal and cervical cancers, continued assessment of this agent with concurrent radiotherapy is warranted in these malignancies as well.

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