Irinotecan in the First-Line Treatment of Colorectal Cancer

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Irinotecan (CPT-11 [Camptosar]) is currently approved for use as a second-line agent in the treatment of metastatic colorectal cancer. Phase II studies have also shown substantial single-agent activity of irinotecan in the

Introduction

Irinotecan (CPT-11 [Camptosar]) is a semisynthetic, water-soluble derivative of the plant alkaloid camptothecin. Based on the results of extensive clinical evaluations,[1] irinotecan received FDA approval for use in fluorouracil-refractory stage IV colorectal cancer. Other potential uses of irinotecan, both in colorectal cancer and in other types of malignancies, are currently under active investigation.

This review will focus on the potential use of irinotecan, either alone or in combination, in the first-line treatment of colorectal cancer. It should be emphasized that these first-line strategies are, at the time of this writing, being actively investigated and are not presently recommended for routine clinical use.

Irinotecan

Irinotecan (CPT-11) is one of several derivatives of camptothecin entering the clinical arena. (The "CPT" in CPT-11 is an abbreviation for camptothecin.) Camptothecin is the active isolate from the stem wood of *Camptotheca acuminata*, a tree that grows throughout most parts of Asia.[2]

Initial clinical trials of irinotecan in the 1970s reported encouraging evidence of antitumor activity; however, substantial and unpredictable toxicities were also encountered.[3-5] This unfavorable toxicity profile caused a loss of clinical interest in the camptothecins until more than a decade later, when the mechanism of action of camptothecin was demonstrated to be the inhibition of the nuclear enzyme topoisomerase I.[6-10]

Knowledge of the target of camptothecin rekindled activity in the development of soluble analogs that could be more practically applied clinically.

One such series of investigations led to the identification of 7-ethyl-10[(4-(1-piperidino)-1-piperidino)-1-carbonyloxy-camptothecin as an agent with good aqueous solubility and a favorable preclinical activity profile.[11-13] Phase I testing of this agent, called CPT-11 at that time, was initiated in Japan[14,15] and subsequently in the United States[16,17] and France.[18] These early phase I trials demonstrated evidence of antitumor activity of irinotecan in advanced, treatment-refractory colorectal cancer patients, leading to an extensive worldwide development program of the drug in this disease.

Treatment of Refractory Colorectal Cancer

Shimada et al published the first phase II study of irinotecan in patients with metastatic colorectal cancer, 81% of whom had fluorouracil-refractory disease.[19] A major objective response rate of 27% was reported in the 63 evaluable patients treated, with a 22% response rate in those who had been treated previously with fluorouracil.

In a subsequent trial conducted in the United States, 43 patients with fluorouracil-refractory colorectal cancer were treated with irinotecan by 90-minute infusion weekly for 4 weeks followed by
a 2-week rest period. This trial reported similar results, with a major objective response rate of 23%.[20] Furthermore, an additional 31% of patients who did not achieve a major response demonstrated either stable disease or a minor clinical regression, increasing the percentage of patients who derived some demonstrable antitumor activity to 54%.

These data were later analyzed in combination with data from two other trials of irinotecan in fluorouracil-refractory colorectal cancer involving a total of 304 patients.[1] The major objective response rate was 13%, with an additional 49% of patients achieving clinical benefit in the form of either a minor response or disease stabilization.

**Treatment of Chemotherapy-Naïve Colorectal Cancer**

Antitumor activity of irinotecan in patients with previously untreated colorectal cancer had been noted in a small population of such patients treated in the initial phase II study by Shimada et al.[19] To more thoroughly investigate this issue, our group at Memorial Sloan-Kettering Cancer Center in New York performed a formal phase II trial of irinotecan in chemotherapy-naïve patients with measurable metastatic colorectal cancer.[21] In this trial, 41 patients received a starting dose of 125 mg/m² of irinotecan weekly for 4 weeks, followed by a 2-week break. We observed a major objective response in 13 patients (32%; 95% confidence interval [CI], 18% to 46%). In addition, 44% of patients demonstrated a lesser degree of antitumor activity, in the form of either a minor response or stable disease. Treatment was reasonably well tolerated, with diarrhea and neutropenia being the major dose-limiting toxicities encountered.

At the time of initiation of the trial, our group was unaware of the work of Abigerges et al demonstrating the utility of an intensive loperamide-based antidiarrheal regimen for the management of irinotecan-induced late-onset diarrhea.[22] Of the first 18 patients treated in our study, 10 (56%) required a dose reduction during therapy. After we became aware of the above-referenced antidiarrheal regimen, we began applying it assiduously. In the remaining 23 patients subsequently started on the trial, this decreased the proportion of those requiring a dose reduction to 9%.

Concurrent with our investigations, a cohort of chemotherapy-naïve colorectal cancer patients received irinotecan in a clinical trial conducted at the Mayo Clinic, using the same starting dose and schedule.[23] This trial reported major objective responses in 8 of 31 patients (26%; 95% CI, 12% to 45%).

European development of irinotecan has focused primarily on the use of a brief infusion given once every 3 weeks. Rougier et al conducted a trial of this once every-3-week schedule in colorectal cancer patients, utilizing a 350 mg/m² starting dose. Of the 213 patients in this trial, 48 had received no prior cytotoxic chemotherapy and 165 patients had progressed after one fluorouracil-based chemotherapy regimen.[24] The response rate to irinotecan in this trial was 18%, with activity rates essentially the same in both chemotherapy-naïve and fluorouracil-refractory patients.

Thus, three independent phase II trials have confirmed the substantial single-agent activity of irinotecan in the first-line treatment of colorectal cancer patients.

**Toxicity**

A consideration of the pros and cons of the use of irinotecan in the first-line treatment of colorectal cancer requires serious consideration of the toxicity profile of irinotecan, and a comparison of this toxicity with that of the fluorouracil-based chemotherapy regimens that are now routinely used in first-line therapy. The two major dose-limiting toxicities of irinotecan are diarrhea and neutropenia.

**Diarrhea**

Diarrhea due to irinotecan can be divided into two distinct syndromes: early-onset diarrhea, which occurs during or shortly after irinotecan administration, and late-onset diarrhea, occurring more than 24 hours after irinotecan administration.
Early-onset diarrhea is the most common manifestation of a cholinergic syndrome that can occur with irinotecan administration. This syndrome is characterized by rapid-onset diarrhea and may also include abdominal cramping and diaphoresis.[25] The syndrome is relatively unusual, however, and, if encountered, is easily managed with atropine. The incidence of previously treated patients reporting grade 3 or 4 diarrhea within 24 hours of irinotecan administration in the pivotal phase II US trials was 8%.[1]

Late-onset diarrhea, while representing a much more serious problem, has become far more manageable now than it was in the earlier irinotecan trials. Late-onset diarrhea was the major dose-limiting toxicity encountered in initial phase I and II trials. This late-onset diarrhea most commonly occurred on approximately day 10 of the treatment cycle.

Two major changes have occurred that have greatly reduced the incidence of late-onset diarrhea. First, investigators and clinicians have become more familiar with irinotecan and its toxicity profile. As doctors become more adept at discerning the early signs of gastrointestinal toxicity and adjusting the irinotecan dose accordingly, the incidence of severe diarrhea has declined.

Perhaps more importantly, based on work initially reported by Abigerges et al,[22] use of an intensive regimen of loperamide has become standard practice in patients treated with irinotecan. The loperamide must be started at the first sign of diarrhea, and taken at a dose of 2 mg every 2 hours (or 4 mg every 4 hours during the night) until the patient has been free of diarrhea for 12 hours. Failure to adhere strictly to this schedule appears to be associated with less successful treatment of the diarrhea.

The overall incidence of dose-limiting diarrhea in the 41 chemotherapy-naïve patients in the trial reported from Memorial Sloan-Kettering was 29%.[21] Of 193 fluorouracil-refractory patients who received the 125 mg/m² starting dose of irinotecan, 65 (34%) developed grade 3 or 4 diarrhea.[1]

To properly assess the importance of late-onset diarrhea with irinotecan, one needs to compare its incidence with that of severe diarrhea in similar patient populations treated with fluorouracil-based regimens. The North Central Cancer Treatment Group (NCCTG) reported a large, multicenter, phase III trial of the two most widely used schedules (in the United States) of fluorouracil plus leucovorin in chemotherapy-naïve colorectal cancer patients.[26] In this trial, dose-limiting diarrhea occurred in 32% of patients receiving weekly fluorouracil plus high-dose leucovorin and in 20% of patients receiving daily × 5 low-dose leucovorin.

Neutropenia

In the Memorial Sloan-Kettering trial of 41 chemotherapy-naïve colorectal cancer patients, 6 (15%) experienced grade 3 granulocytopenia and 3 (7%) experienced grade 4.[21] Only one patient (2%) developed neutropenic fever. In the Mayo Clinic study of 31 previously untreated colorectal cancer patients, 9% developed grade 4 neutropenia and 3% experienced neutropenic fevers.

In the pooled analysis of 304 fluorouracil-refractory colorectal cancer patients treated with irinotecan in phase II trials, grade 4 neutropenia was seen in 12% of patients and 3% developed neutropenic fever.[1] One treatment-related death (0.3%), which was due to neutropenic sepsis, occurred in these 304 patients. This death rate compares favorably with the seven treatment-related deaths in 372 patients (1.9%)[26] and eight deaths in 620 patients (1.3%)[27] reported in two large multicenter trials of first-line fluorouracil-based chemotherapy in colorectal cancer patients.

What Role Should Irinotecan Play in First-Line Therapy?

Although phase III data directly comparing irinotecan with fluorouracil plus leucovorin have not yet been reported, a review of the phase II toxicity and activity profiles of irinotecan in chemotherapy-naïve colorectal cancer patients suggests that these profiles are comparable to those seen with commonly used schedules of fluorouracil plus leucovorin in multicenter phase III trials. As such, consideration of the use of irinotecan monotherapy in the first-line setting does appear to be...
clinically defensible.

Economic issues may strongly militate against the routine use of single-agent irinotecan as first-line therapy, however. The cost of irinotecan is well in line with the costs of other newer anticancer agents, such as paclitaxel (Taxol), docetaxel (Taxotere), vinorelbine (Navelbine), and gemcitabine (Gemzar). However, at present, the cost of irinotecan is several orders of magnitude higher than the cost of generic fluorouracil and leucovorin, and the limited data available thus far suggest the equivalence, rather than the superiority, of irinotecan. Given the current emphasis on cost containment in the worldwide health care community, it is unlikely that single-agent irinotecan will gain favor as a general first-line regimen in the absence of additional data, including direct comparative phase III data.

**Incorporation Into Combination Regimens**

How then, might irinotecan be usefully incorporated into first-line management? One promising possibility is through the incorporation of irinotecan into fluorouracil-containing combination regimens. Our group at Memorial Sloan-Kettering Cancer Center has reported a phase I trial utilizing full-dose (125 mg/m²) weekly irinotecan combined with 500 mg/m² of fluorouracil and 20 mg/m² of leucovorin, with all drugs given weekly for 4 consecutive weeks followed by a 2-week break.[28]

This combination schedule is now being compared with fluorouracil plus leucovorin (daily × 5 low-dose leucovorin schedule) in a multicenter, multinational phase III trial. A third arm of this trial is treating patients with single-agent irinotecan alone. Thus, the efficacy and toxicity of the irinotecan/fluorouracil/leucovorin regimen will be directly compared to irinotecan alone and to a standard fluorouracil-based treatment. This trial will provide an accurate randomized comparison of these three approaches, and will likely shed considerable light on the role, if any, of irinotecan, either alone or in combination, in the first-line treatment of colorectal cancer.

Other schedules of irinotecan/fluorouracil combinations have now been reported,[29-31] and several of these have also recently entered phase III trials.

**Adjuvant Treatment of Stage III and High-Risk Stage II Patients**

Ultimately, the primary role of irinotecan in first-line treatment of colorectal cancer may well lie in the postsurgical (adjuvant) treatment of stage III and high-risk stage II patients. Conceivably, phase III combination therapy trials may show that initial response rates are higher with irinotecan/fluorouracil combinations than with either drug alone. Such higher response rates could translate into higher postsurgical cure rates, as responses in the setting of minimal microscopic residual disease could result in a higher degree of complete disease eradication.

We have now begun to explore both concurrent and sequential administration schedules of irinotecan plus fluorouracil and leucovorin for resected stage III and high-risk stage II colon cancer patients. Based on our prior phase I study of daily low-dose irinotecan,[32] we are also studying the use of concurrent daily irinotecan plus pelvic radiation as a preoperative treatment regimen for locally advanced rectal cancer.

**Rational Selection of Patients for First-Line Irinotecan**

The ability to accurately predict whether or not an individual patient responds to one chemotherapeutic regimen or another would clearly improve the palliation of patients with metastatic disease, and would potentially have important implications for directing adjuvant treatment for high-risk resected patients. Recent data indicate that a high relative expression of thymidylate synthase messenger RNA (mRNA), as determined by quantitative reverse transcriptase-polymerase chain reaction (RT-PCR), strongly predicts for failure to respond to fluorouracil/leucovorin.[33] Further preliminary data from Danenberg et al suggest that low expression of thymidine phosphorylase is consistent with responsiveness to fluorouracil/leucovorin, while high expression of either thymidylate synthase or thymidine phosphorylase correlates with resistance to these agents.[34]
Because irinotecan has been shown to be active in some patients with colorectal cancer, we now have, for the first time, a viable treatment alternative to fluorouracil-based regimens. Preliminary data have also indicated that some patients who respond to irinotecan have tumors with high thymidylate synthase expression, above the levels consistent with responsiveness to fluorouracil.[35] Furthermore, increased gene expression of topo-I, the gene that codes for the target enzyme of irinotecan, appears, on the basis of a small study, to correlate with sensitivity to irinotecan.[35]

Thus, it may be possible, through the use of these and other selective molecular determinants of response, to identify prospectively those patients who are more likely to benefit from fluorouracil-based treatments, as well as those who are unlikely to benefit from fluorouracil and, thus, may be more appropriate candidates for first-line irinotecan therapy. Clinical trials to investigate this approach are now underway at our institution and in advanced planning stages elsewhere.

**Conclusions**

Currently, irinotecan is approved for the second-line therapy of metastatic colorectal cancer. Data from phase II trials, however, have demonstrated substantial antitumor activity of irinotecan in the first-line treatment of this disease. Diarrhea and neutropenia are the major dose-limiting toxicities, although in appropriately selected patients, these toxicities are usually manageable. Moreover, their frequency and severity appear to be similar to those of conventional fluorouracil-based regimens.

Phase III data directly comparing irinotecan to fluorouracil plus leucovorin are not yet available. In the absence of data clearly demonstrating the superiority of irinotecan over standard first-line fluorouracil plus leucovorin, the routine use of irinotecan in the first-line treatment of colorectal cancer is unlikely to become accepted practice, due, at least in part, to the higher cost of irinotecan.

Combination regimens of irinotecan plus fluorouracil have been developed, and phase III trials of these regimens in the first-line treatment of colorectal cancer are in progress. Ongoing studies are also exploring the role of irinotecan-based combinations in the adjuvant treatment of earlier stage colon and rectal cancers. These combination strategies, incorporating irinotecan into first-line multidrug regimens, may yield benefits that warrant the inclusion of irinotecan in the initial treatment of colorectal cancer. In addition, prognostic molecular determinants of response may, in the near future, provide a rational basis for selecting appropriate patients for first-line irinotecan monotherapy.

**References:**


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