Improving the Toxicity of Irinotecan/5-FU/ Leucovorin: A 21-Day Schedule

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Irinotecan (CPT-11, Camptosar) is one of the new generation of chemotherapeutic agents that has activity in advanced colorectal cancer. It has antitumor efficacy as a single agent, and also has been combined with fluorouracil (5-FU) and leucovorin (IFL) to treat these patients. Randomized studies have confirmed the superiority of IFL to 5-FU and leucovorin alone with regard to patient survival, time to progression, and tumor response rate. The optimal schedule for combining these agents remains uncertain, but in the United States, the schedule of IFL weekly for 4 consecutive weeks repeated every 6 weeks, according to the schedule reported by Saltz et al, has been widely used, although with some toxicity (especially myelosuppression and diarrhea). In an attempt to improve the tolerability of IFL, some have advocated modifying the schedule of IFL to weekly for 2 weeks, with repeated cycles every 21 days. Twenty-three patients with advanced colorectal cancer have been treated on this schedule at a single institution. Therapy was well tolerated, with 35% of patients experiencing grade 3/4 neutropenia, two of whom had episodes of febrile neutropenia, and 9% with grade 3/4 diarrhea. The median relative dose intensity of irinotecan administered in the first 18 patients treated with this regimen was 94%. These data support the hypothesis that modifying the schedule of administration of IFL improves the tolerability and ability to deliver the regimen, but must be confirmed by randomized prospective studies, which may also attempt to evaluate the role of bolus 5-FU in the treatment of advanced colorectal cancer.

Irinotecan (CPT-11, Camptosar) is a semisynthetic derivative of camptothecin sodium, which itself is the active extract from the bark of the Chinese/Tibetan deciduous tree Camptotheca acuminata (Nyssaceae family). Although early development of this camptothecin was stymied by the toxicity of the compound, in particular myelosuppression and hemorrhagic cystitis, irinotecan has been much better tolerated, with the primary toxicities being myelosuppression and diarrhea.[1] Subsequent studies in humans have demonstrated that irinotecan has activity in a number of malignancies, including colorectal,[ 2,3] gastroesophageal,[4-6] pancreatic,[ 7] lung,[8,9] breast,[10] and gynecologic cancers.[11,12] In the Unite States, irinotecan is currently indicated for use in patients with advanced colorectal cancer. In 1998, two studies proved the benefit of irinotecan in patients with advanced colorectal cancer that had progressed despite prior therapy with the then-standard therapy, fluorouracil (5-FU). Cunningham et al[13] reported that salvage irinotecan (n = 189) at 300 to 350 mg/m² intravenously (IV) every 3 weeks significantly increased 1-year survival in comparison to supportive care alone (n = 90): 36.2% compared to 13.8%. In the same patient population, Rougier et al[14] randomized 267 patients to 300 mg/m² of irinotecan every 3 weeks or infusional 5-FU. Again, the 1-year and median survivals were increased in patients treated with irinotecan (n = 133), at 45% and 10.8 months vs 32% and 8.5 months, respectively.[14] Other studies confirmed that irinotecan has antitumor activity in patients without previous chemotherapy for metastatic colorectal cancer.[2,3,15,16] As a result, irinotecan has become widely accepted for use in patients with metastatic colorectal cancer.
Irinotecan and 5-FU Based on the differing mechanisms of activity of the two most active antineoplastic agents in colorectal and other gastrointestinal cancers, these drugs-irinotecan and 5-FU-have been administered together. A number of methods of combining irinotecan and 5-FU with leucovorin (IFL) have been evaluated, but the optimal combination and schedule remain uncertain (Table 1). Given the multitude of 5-FU treatment schedules used around the world, this is not surprising. However, the most widely used combinations of irinotecan and 5-FU are based upon a bolus administration of therapy. In a phase I study, Saltz et al[17] combined irinotecan, 5-FU, and leucovorin in a weekly for 4 weeks schedule, with cycles repeated every 6 weeks (therapy administered on days 1, 8, 15, and 22 every 42 days). Sequential escalations of 5-FU, then irinotecan, were performed, and the doses recommended for further evaluation were 125 mg/m² of irinotecan infused IV over 90 minutes, 500 mg/ m² of 5-FU by bolus, and 20 mg/m² of leucovorin by IV bolus. The primary dose-limiting toxicity was neutropenia, although diarrhea was common.[17] Furthering the evaluation of this promising combination, Saltz et al[18] reported a study of 683 patients who were randomized to either weekly IFL with this schedule (n = 231), 5-FU and leucovorin on the Mayo clinic schedule (n = 226), or irinotecan at 125 mg/m² IV for 4 consecutive weeks (n = 226), again followed by a 2-week break. This study demonstrated a significant superiority of IFL in median progression-free survival, objective response rate, and median survival. In particular, therapy with IFL resulted in a 36% decrease in risk of progression, and a 22% decrease in risk of death in comparison to the previous standard therapy, 5-FU and leucovorin.[18] The so-called de Gramont regimen has been an accepted standard combination of 5-FU and leucovorin for advanced colorectal cancer in France.[19] A simplified version of this regimen, with the 5-FU administered as a 400 mg/m² IV bolus, followed by a 46-hour continuous infusion at 2,400 to 3,000 mg/m², every 2 weeks, has been combined with 180 mg/m² irinotecan on the first day of therapy (FOLFIRI), in a study reported by Andre et al.[20] As salvage therapy, limited antitumor activity was noted. In 33 treated patients, two (6%) patients had partial responses and 20 experienced stabilization of disease. Therapy was well tolerated, with 15% of patients experiencing severe vomiting and myelosuppression, and severe diarrhea seen in 12%.[20] The popular German Arbeitsgemeinschaft Internische Onkologie (AIO) schedule of high-dose 5-FU administered as a 24-hour infusion weekly has also been combined with irinotecan. Vanhoefer et al[21] delivered the full dose of 5-FU (2,600 mg/ m² weekly) and leucovorin (500 mg/ m²) with 80 mg/m² of irinotecan. The dose-limiting toxicity was severe diarrhea; however, myelosuppression was not a significant problem.[21] Other researchers have evaluated further combinations of the agents. Falcone et al[22] combined a 48-hour continuous infusion of 5-FU (3,500 mg/m²) with irinotecan in 33 patients, evaluating irinotecan both preceding and following 5-FU. Cycles prior to 5-FU and leucovorin permitted a higher dose of irinotecan administration (recommending a dose of 350 mg/m²) in this combination, with less toxicity overall than the reverse schedule. Severe neutropenia was noted in 22% of patients, and grade 3/4 diarrhea in 4%.[22] In a phase I study in 42 patients...
with metastatic colon cancer, Kakolyris et al[23] combined a 4-day continuous infusion of 5-FU with irinotecan immediately afterwards. The doses recommended for subsequent evaluation were 600 mg/m²/d and 350 mg/m², respectively. At these doses, 20% of 25 cycles reported grade 3/4 neutropenia, and dose-limiting toxicities were noted in two of six patients: severe neutropenia with severe diarrhea, and neutropenic fever.[23] Capecitabine (Xeloda), an oral fluoropyrimidine, was found to have superior activity and less toxicity in comparison to bolus 5-FU and leucovorin administered on the Mayo clinic schedule.[24,25] Because of its ease of administration and good toxicity profile, capecitabine has been combined with irinotecan, with promising results. Several schedules have been evaluated. Cassata et al[26] combined 1,000 mg/m² of capecitabine twice daily for 14 days with irinotecan, with the latter administered either as 300 mg/m² on day 1 or 150 mg/m² on days 1 and 8 of each 21-day treatment cycle. Both schedules were fairly well tolerated, and active in the first-line treatment setting (71% overall response [15/21]).[26] Others have evaluated similar schedules and slightly lower irinotecan doses yielding similar findings with regard to efficacy, as well as a suggestion of somewhat better toxicity profiles.[27,28]. On the former schedule, Delord et al[29] used 250 mg/m² of irinotecan on day 1 of treatment, and reported grade 3 neutropenia in two of seven patients, and grade 3 diarrhea in one patient. As part of a randomized phase II study, Jordan et al[30] treated advanced colorectal cancer patients with irinotecan at 100 mg/m² on days 1 and 8 of each 21-day treatment cycle. Severe diarrhea was reported in three and severe neutropenia in two of the 28 patients. However, two patients died from neutropenic sepsis with diarrhea and pulmonary embolism, respectively.[30] Despite evaluations of these various schedules, the preferred combination of irinotecan and 5-FU remains uncertain. The schedules that have been the most intensely evaluated to date are the weekly IFL schedule, and irinotecan in combination with some variation of the bimonthly de Gramont schedule.

**Efficacy**

The superior antitumor activity of IFL in comparison to 5-FU and leucovorin administered by the Mayo or de Gramont schedules, as well as irinotecan alone in patients with metastatic colorectal cancer with no prior chemotherapy for metastatic disease, was established by two reports published in 2000. The first by Saltz et al,[18] in the *New England Journal of Medicine* as described above, demonstrated superior response, time to progression, and survival with the addition of irinotecan to 5-FU and leucovorin in comparison to irinotecan alone, or 5-FU and leucovorin administered according to the Mayo clinic schedule. Similarly, Douillard et al[31] randomized 387 patients to one of two 5-FU/leucovorin treatment regimens (de Gramont schedule with this schedule [288 patients] or AIO schedule [97 patients] at the investigator's discretion) with or without irinotecan. Irinotecan was administered at either 180 mg/m² IV on day 1 of therapy every 2 weeks with the de Gramont schedule, or 80 mg/m² IV weekly. Again, irinotecan significantly increased the response rate ($P < .001)$, time to progression ($P < .001$), and median survival ($P < .031$) in comparison to patients treated with 5-FU and leucovorin alone, regardless of the schedule employed.[31] With these studies demonstrating the efficacy of IFL, this combination subsequently became the standard initial therapy for patients with metastatic colorectal cancer. Although the preferred combination was uncertain, in the United States the weekly schedule was most widely used, in part because of the ease of administration. However, subsequent reports have raised concerns about the tolerability of this schedule.

**Toxicity**

Not surprisingly, the toxicity profile of IFL depends in great part on the schedule of 5-FU administered with irinotecan (Table 2). The weekly IFL toxicities reported by Saltz et al[18] in the phase III study were primarily myelosuppression, with 53.8% of patients experiencing grade 3/4 neutropenia, and neutropenic fevers in 7.1%. Severe or life-threatening diarrhea was also a prominent toxicity, occurring in 22.7% of patients, and grade 3/4 nausea/vomiting in 9.7%. Overall though, therapy was considered to be well tolerated, with only 2 (0.9%) of 225 patients dying as a consequence of therapy.[18] With the combination of the de Gramont schedule of 5-FU and leucovorin with irinotecan administered every other week, grade 3/4 neutropenia remained the most common toxicity, occurring in 46.2% of patients, with neutropenic fever in 5.5% of patients. Severe diarrhea occurred in 13.1% of patients, and grade 3/4 nausea/vomiting in about 3% of patients. When combined with 5-FU and leu-
administered on the AIO schedule, IFL resulted in somewhat more toxicity, including severe diarrhea in 44.4% and vomiting in 11.1% of the 54 patients treated. Grade 3/4 neutropenia was reported in 28.8%, and febrile neutropenia in 9.3%. This difference in toxicities among these regimens was most likely a consequence of the 5-FU/leucovorin schedule employed, and the resultant difference in irinotecan schedule. Again, the regimens appeared to have a similar efficacy, despite the difference in toxicity. With the combination of irinotecan, 5-FU, and leucovorin becoming the standard therapy for patients with metastatic colorectal cancer, its use in the late 1990s and early 21st century escalated dramatically. In the United States, the weekly regimen of IFL, the so-called Saltz regimen, had become the predominant schedule employed because of the relative ease of administration, which did not require the placement of prolonged venous access. However, dramatic reports from two Intergroup studies—Cancer and Leukemia Group B (CALGB) 89803 and North Central Cancer Treatment Group (NCCTG) 9741—evaluating the efficacy of this schedule of IFL in the respective adjuvant and metastatic settings have led to renewed concerns about the tolerability of this regimen
(Table 3). In April 2001, the External Data Monitoring Committee for NCCTG 9741 reported deaths within the first 60 days of study entry in 13 (4.5%) of 289 patients. A subsequent review of the CALGB study found that 16 (2.5%) of 635 patients treated with IFL also died within 60 days of initiating treatment. Of interest, the initial report of IFL in a phase III study noted that 0.9% of 225 patients died from drug-related causes, compared to 1.4% of 219 patients treated with bolus 5-FU/leucovorin on the Mayo Clinic schedule. The deaths that occurred on this study were later reviewed, and the 60-day mortality, the same yardstick applied to the Intergroup studies, revealed rates of 6.7% with IFL and 7.3% with 5-FU/leucovorin.[32] An independent review of these deaths attributed them to "gastrointestinal syndrome," including diarrhea, nausea, vomiting, abdominal cramping leading to dehydration and electrolyte abnormalities, and often in the setting of neutropenia, fever, or infection; or "vascular syndrome," including myocardial infarction, pulmonary embolism, or cerebrovascular accidents. The gastrointestinal syndrome was felt to cause, exacerbate, or contribute to the deaths of 12 patients in the CALGB study and 6 in the NCCTG study. The vascular syndrome was believed to cause or contribute to the deaths of five patients in the CALGB study and three in the NCCTG study. The panel found that the median age of the patients treated with IFL who died was 69.5 years in CALGB 89803 and 65 years in NCCTG 9741, older than the median ages of patients typically enrolled in studies of colorectal cancer. A number of recommendations were made by this expert panel, including close monitoring of patients treated with IFL, especially older patients, and an aggressive approach to the treatment of diarrhea and abdominal cramping, including aggressive use of antibiotics in patients with diarrhea and neutropenia.[33] In addition to the concerns about the toxicities of weekly IFL, another difficulty of the regimen is that severe toxicities occurred despite a relatively low dose intensity of chemotherapy. In particular, great difficulty was encountered in administering weeks 3 and 4 of chemotherapy because of myelosuppression and diarrhea. As a result, the median relative dose intensities (calculated by dividing the actual dose of the agent delivered by the intended dose of the agent) of irinotecan and 5-FU were 72% and 71%, respectively.[18] **21-Day Schedule**

Considering the difficulties of dose delivery and toxicity in weekly IFL according to the Saltz schedule, which appeared to be cumulative within a cycle, one manner of improving the therapeutic index of weekly IFL would seem to be to create a break after the second week of therapy, prior to resuming IFL. To evaluate this hypothesis, 23 patients have been treated with weekly IFL at the Lombardi Cancer Center at Georgetown University Medical Center. However, therapy was administered on days 1 and 8 every 21 days. For patients who were 75 years or older, the initial dose of irinotecan was 100 mg/m². The planned dose intensity of this schedule would be identical to the Saltz schedule of IFL. The patient population was similar to other studies of patients with ad-
advanced colorectal cancer (Table 4). However, none of the patients had received prior chemotherapy. All patients had a good performance status (Eastern Cooperative Oncology Group 0 or 1). The median age of the population was 57 years, encompassing a range of ages from 38 to 77; two patients were 75 years or older. Fourteen of the patients were males. Fifteen of the patients were given chemotherapy as adjuvant treatment. Only eight of these patients received therapy as treatment for measurable metastatic disease. One patient has received 6 weeks of therapy and is not yet evaluable for response. Three of the other seven had stable disease, and four had progression of disease on their follow-up evaluation. This schedule was well tolerated, with grade 3/4 neutropenia occurring in eight (35%) patients, and severe diarrhea in only two (9%). Two patients experienced one episode each of febrile neutropenia with the first cycle of therapy, but tolerated further treatment with IFL on the 21-day schedule after a 25% dose reduction. No other grade 3/4 toxicities were noted (Table 5). Supporting these data that demonstrate the tolerability of this schedule of IFL was the ability to deliver the therapy. In the first 18 patients treated with this schedule, the median relative dose intensities, calculated by the same method as Saltz et al,[18] of irinotecan and 5-FU were 94% and 92% (Table 6). Half of these patients received therapy without requiring any dose modifications. Full doses were administered in 104 of 141 cycles, with a 10% dose reduction occurring in 26 cycles (18.4%), and 25% and 50% dose reductions in 9 and 2 cycles, respectively. These results, especially with regard to the ability to deliver a high dose intensity of the regimen with a simple modification of the schedule of administration, support the hypothesis that altering the schedule of therapy will improve the therapeutic index of IFL. However, because of the potentially confounding differences between study populations, the comparison of median relative dose intensity between these two study groups requires confirmation in a prospective randomized study. Furthermore, the change in the schedule may not be the only, or primary, reason for the ability to deliver such a high proportion of the intended dose. In particular, the patient population must be considered to be favorable. First, the median age of the treated patients was 57 years, with only two patients being over 75, and thus may be considered inadequately representative of the population of patients with advanced colorectal cancer. Moreover, as many of the patients who were treated in this program had only a high risk for disease recurrence, and essentially received adjuvant therapy, they may have been a "healthier" population overall. The antitumor activity and tolerability of the 21-day schedule of IFL, then, can only be assessed in the context of a prospective randomized trial.
Future Directions

At the 2002 meeting of the American Society of Clinical Oncology, Goldberg et al.[34] reported the preliminary results of NCCTG 9741. A total of 795 patients with advanced colorectal cancer were randomized to weekly IFL using the Saltz schedule as the control arm, or oxaliplatin (Eloxatin), 5-FU, and leucovorin on the de Gramont schedule (FOLFOX 4), or a combination of irinotecan and oxaliplatin every 3 weeks. The median progression-free survival and median overall survival were significantly longer for patients treated with FOLFOX 4 than IFL on the Saltz schedule, at 8.8 vs 6.9 months, and 18.6 compared to 14.1 months, respectively.[34] As a result of these findings, the US Food and Drug Administration approved oxaliplatin in August 2002 for use in combination with infusional 5-FU and leucovorin for the treatment of patients with advanced colorectal cancer. An additional question is whether oxaliplatin-based chemotherapy will become the new standard first-line therapy for patients with metastatic colorectal cancer. Irinotecan, oxaliplatin, and 5-FU possess activity in advanced colorectal cancer, and should be made available to all. However, the appropriate combination and best sequence of these agents will need to be elucidated, including the optimal method of administering 5-FU (ie, bolus, infusional, or oral) (Figure 1). Finally, the potential role of the targeted therapies, such as the epidermal growth factor receptor (EGFR) antagonists including erbitux (C-225),[35] gefitinib (ZD1839, Iressa), and OSI- 774 (Tarceva), and vascular endothelial growth factor antagonists including bevacizumab,[36] are being evaluated. About 70% of patients with colorectal cancer have tumors that overexpress EGFR, making this a promising target for intervention. Preliminary studies have suggested that the combination of irinotecan and erbitux has activity in patients with metastatic colorectal cancer. The precise contribution of erbitux in this combination, as well as the optimal method of combining chemotherapy and these targeted therapies, also remain unknown [35]. With a plethora of other
potential targets and agents against these targets being identified and developed, a variety of options may be available for patients in the future, offering an opportunity to tailor therapy to the patient, maximize activity, and minimize toxicity. A modification of the weekly bolus IFL, altering the schedule to administer therapy on days 1 and 8 every 21 days, may improve the therapeutic index of IFL and allow physicians to continue offering patients a relatively easily delivered and effective chemotherapy regimen, and encourage investigators to explore the regimen as a backbone to further study of new agents and combinations in the treatment of advanced colorectal cancer.

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