European Experience With Irinotecan Plus Fluorouracil/Folinic Acid or Mitomycin

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Tremendous progress has been made in the medical treatment of advanced colorectal cancer during the past 2 to 3 years, due to the availability of several new drugs. Of these new agents, irinotecan (CPT-11 [Camptosar]) seems

Introduction

During the past few years, tremendous progress has occurred in chemotherapy for colorectal cancer, as reflected in the numerous chemotherapy trials that are ongoing or planned. Several new drugs have shown activity in advanced disease, adding treatment alternatives to fluorouracil (5-FU), which has been the sole agent for advanced colorectal cancer for almost 40 years. These drugs include irinotecan (CPT-11 [Camptosar]), raltitrexed (Tomudex), oxaliplatin, and capecitabine (Xeloda). This article will focus on irinotecan, which has demonstrated activity as a single agent in several phase II studies in Europe, Japan, and the United States. Two large, randomized, multicenter studies established its superiority over best supportive care and other second-line chemotherapy regimens.[1,2] These data indicate that irinotecan should be integrated rapidly into combined protocols for advanced colorectal cancer.

In this article, we will present the results of ongoing or recently published European trials of irinotecan-based combinations, mainly irinotecan combined with 5-FU alone; 5-FU plus folinic acid (leucovorin); or mitomycin (Mutamycin). Other articles in this monograph will review the results achieved with irinotecan alone or combined with other drugs (ie, oxaliplatin or raltitrexed).

Irinotecan Plus 5-FU Alone

Two protocols combining irinotecan with 5-FU alone have been tested in Europe; the Mayo Clinic schedule and the Lokich schedule.

Mayo Clinic Schedule

A study performed at the Salpêtrière Hospital in Paris[3] was aimed at evaluating the feasibility and safety profile of irinotecan combined with 5-FU administered as a daily intravenous (IV) bolus injection for 5 consecutive days. A secondary aim was to study the pharmacokinetic interaction between the two drugs. This open-label, single-center, phase I study with dose escalation included 41 patients with advanced solid tumors (29 with colorectal cancer, 5 with other gastrointestinal tumors, and 7 with other solid tumors). Patients were treated with at least two 4-week cycles, one in which irinotecan was administered before the 5 days of 5-FU and the other in which irinotecan was given on day 6 (Figure 1).

Neutropenia was the dose-limiting toxicity. Grade 3 or 4 neutropenia occurred in 5 of 6 patients treated at the 5-FU/irinotecan dose level of 375/350 mg/m². The other maximum tolerated dose (MTD) was achieved at a 5-FU/irinotecan dose level of 450/300 mg/m²; this dose level resulted in grade 3 or 4 neutropenia in four of four patients. Other toxicities included mild diarrhea, fever, anemia, and thrombocytopenia. Based on this study, the recommended doses were 300 mg/m² of irinotecan and 375 mg/m² of 5-FU.

The pharmacokinetic analysis showed no statistically significant differences in clearance of either irinotecan or its active metabolite, SN-38, regardless of whether irinotecan was given before or after 5-FU. However, when irinotecan was given before 5-FU, a minor pharmacokinetic interaction between irinotecan and 5-FU was observed, resulting in statistically lower 5-FU catabolism (Table 1). This finding indicated that irinotecan should be given before 5-FU.
Lokich Schedule
In a phase I study conducted in Spain by Paz-Ares et al,[4] irinotecan was given over 90 minutes on
day 1, followed by a 14-day infusion of 5-FU (250 mg/m²/d), with cycles repeated every 3 weeks. The
study involved 11 patients with advanced solid tumors (4 of whom had colorectal cancer; 2,
esophageal cancer; 2, head and neck cancer; and 3, other solid tumors). To date, four doses of
irinotecan have been tested: 150, 175, 200, and 250 mg/m².
No dose-limiting toxicity has been reported yet, but the main toxicity is diarrhea. Mild nausea,
vomiting, malaise, and alopecia also have been reported. Minor responses and disease stabilization
have been observed, but no partial or complete responses have been noted.

Irinotecan Plus 5-FU and Folinic Acid
The high activity of the combination of 5-FU and folinic acid (FUFOL) in advanced colorectal cancer is
now unquestionable. These results make the two drugs attractive candidates for irinotecan-based
combinations. Four such combinations have been tested in Europe.

Alternating Irinotecan and FUFOL
Preliminary results of a multicenter study of irinotecan alternated with FUFOL, performed in Italy,
were recently presented by Barone et al.[5,6] As shown schematically in Figure 2, 5-FU 425 mg/m²/d
was administered as an IV bolus injection that was repeated for 5 consecutive days, according to the
Mayo Clinic schedule. Low-dose folinic acid (20 mg/m²/d) was also injected as a daily bolus for 5
consecutive days. Irinotecan 350 mg/m² was administered as a 90-minute infusion on day 1. One
21-day cycle of irinotecan was alternated with one 21-day cycle of FUFOL. The study included 33
colorectal cancer patients receiving first-line chemotherapy for metastatic disease.
Neutropenia (20%) and diarrhea (20%) were the main toxicities encountered. However, the
combination was relatively well tolerated. Of the 133 cycles evaluated for toxicity, only 14 cycles had
to be delayed and 11 required a dose reduction due to toxicity. Of the 29 patients evaluable for
response, 9 showed a partial remission (31%) and 4 exhibited a minor response.

Weekly Irinotecan and FUFOL
A phase I study of weekly irinotecan and FUFOL was conducted in Germany. As reported by
Vanhoefer et al[7] in Amsterdam in October 1997, this study included 26 patients receiving first-line
therapy for advanced colorectal cancer. Seven dose levels, administered over 4 or 6 weeks (Figure 3
), were evaluated. Irinotecan was given over 90 minutes on day 1 of a weekly cycle at doses ranging
from 80 to 100 mg/m². Folinic acid 500 mg/m² was administered over 2 hours, followed by a 24-hour
infusion of 5-FU given at doses ranging from 2 g/m²/wk for 4 weeks to 2.6 g/m²/wk for 6 weeks.
Based on their findings, these authors recommended irinotecan 80 mg/m², folinic acid 500 mg/m²,
and 5-FU 2.6 g/m², given for 6 consecutive weeks, followed by 1 week of rest.
The main toxicities were gastrointestinal. Eleven patients had World Health Organization (WHO)
grade 2 or higher vomiting and 2 patients had WHO grade 2 or higher diarrhea. However, out of 17
patients evaluable for response, 11 (61%) had a partial response.

Irinotecan Combined With LV/5-FU2
Another FUFOL regimen combines irinotecan with folinic acid (leucovorin) and a double dose (bolus
and infusion) of 5-FU (LV/5-FU2). This regimen, also called the "de Gramont schedule," was
compared to irinotecan alone in a large French phase I/II study reported by Rougier et al.[8,9] The
study involved 46 patients with advanced colorectal cancer who had received one or more prior
chemotherapy regimens.
As shown in Figure 4, these patients were treated with a 90-minute infusion of irinotecan given at
increasing doses starting at 100 mg/m². After 1 hour, folinic acid (200 mg/m²/d) was infused over 2
hours on days 1 and 2; on both days, folinic acid was followed by 5-FU given as a bolus injection (400
mg/m²/d) and as a 22-hour continuous infusion (600 mg/m²/d). To date, seven doses of irinotecan
have been evaluated: 100, 120, 150, 180, 200, 220, and 300 mg/m².
No dose-limiting toxicity has been reported as yet; the 300-mg/m² dose level is still being tested.
However, some delayed diarrhea, nausea, vomiting, and severe asthenia have been observed.
Among 50 evaluable patients, 2 complete response and 8 partial responses have been achieved
(overall response rate, 22%).

Irinotecan Plus Simplified LV/5-FU2 Regimen
An ongoing phase II study being performed by de Gramont et al under the auspices of the
GERCOD-MARMHIC French collaborative group is testing the combination of irinotecan plus a
simplified LV/5-FU2 regimen.[10] The treatment plan is very similar to the LV/5-FU2 protocol
described above, except the daily bolus of 5-FU is omitted.
This study is being conducted in colorectal cancer patients who have been heavily pretreated (more than two previous chemotherapy regimens). Although it is too early for results to be evaluated, responses and disease stabilization apparently have been observed. Among 34 evaluable patients, there have been 2 partial responses (6%).

**Irinotecan Plus Mitomycin**

Mitomycin is another active compound in the treatment of gastrointestinal tract tumors, including advanced colorectal cancer. A study evaluating the combination of mitomycin and irinotecan was recently completed at the Salpêtrière Hospital in Paris[11,12] in collaboration with Professor H. Bismuth and colleagues at the Center for Hepatobiliary Disease, Paul Brousse Hospital. This phase I/II study involved 26 patients with advanced gastrointestinal tumors (22 with colorectal cancer, 2 with pancreatic cancer, and 2 with cholangiocarcinoma). Four dose levels of irinotecan/mitomycin were evaluated: 300/8, 325/8, 350/8, and 325/10 mg/m\(^2\). Mitomycin was injected as an IV bolus, and irinotecan was administered as a 90-minute infusion; cycles were repeated every 21 days. The dose-limiting toxicity was hematologic; five cases of grade 3-4 neutropenia and two of grade 3-4 thrombocytopenia were observed among six patients treated at the highest dose level. The recommended doses, therefore, were 325 mg/m\(^2\) of irinotecan and 8 mg/m\(^2\) of mitomycin. Other toxicities included diarrhea, infection, immunoallergic pneumopathy, and one case of delayed hemolytic-uremic syndrome.

Responses were observed at each dose level, although all but one patient had been pretreated. There were a total of three complete responses (at 6, 6, and 9 months, respectively) and three partial responses.

**Conclusions**

Several combination regimens tested in Europe during the past 2 years have attempted to incorporate irinotecan into more classic cytotoxic regimens for advanced colorectal cancer. These regimens have included the combination of irinotecan with: (1) 5-FU alone, given as a bolus or protracted infusion; (2) 5-FU modulated by folinic acid, using different combinations of the two drugs; or (3) mitomycin.

In each of these studies, clinical activity has been observed in patients with advanced disease, including those who had been heavily pretreated. Response rates ranging from 29% to 61% have been reported, with a few cases of complete remission. The toxicity of these combinations seems to be relatively acceptable. Neutropenia and gastrointestinal toxicities are the most frequently encountered side effects.

The superiority of these irinotecan-based combination regimens over the same 5-FU or 5-FU/folinic acid regimens without irinotecan has yet to be demonstrated, however. Several large, multicenter, phase III studies have recently been initiated in Europe and other parts of the world in order to confirm the potential benefit of these combination regimens. The preliminary results of these studies should be available within a year.

**References:**


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