

Irinotecan: a new treatment in metastatic colorectal cancer

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Objective. Historically, outcomes of metastatic colorectal cancer therapy have been disappointing, with fluorouracil (5-FU) producing response rates of no more than 15%. The addition of leucovorin increases response rates; however, survival rates are largely unaffected. Recently, the topoisomerase I inhibitor, irinotecan, has proved active in metastatic colorectal cancer and is indicated as second-line therapy following disease recurrence or progression after 5-FU-based therapy. More recently, irinotecan plus 5-FU-LV was compared with 5-FU-LV as first line treatment of colorectal cancer, showing impressive results. This article discusses the role of irinotecan, as a single agent and in combination with 5-FU-LV, in the treatment of advanced colorectal cancer.

Data sources. A MEDLINE search was conducted using 5-fluorouracil, irinotecan, leucovorin, and metastatic colorectal cancer as primary search terms. Reference lists, bibliographies of pertinent articles, and abstracts from the American Society of Clinical Oncology and the European Society for Medical Oncology annual meetings were also identified and reviewed. Clinical literature was reviewed and analyzed.

Data synthesis. Results of studies comparing irinotecan with continuous infusion 5-FU or best supportive care suggest that irinotecan is superior to either treatment as second-line therapy of metastatic colorectal cancer. Based on these study results, along with irinotecan's lack of cross-resistance with other chemotherapy agents and mechanism of action that differs from 5-FU, phase III trials evaluating the use of irinotecan in combination with 5-FU-LV as first-line treatment for advanced colorectal cancer were conducted. The results of a pivotal trial evaluating irinotecan plus 5-FU-LV in this setting show superior response rates (RRs), time to tumor progression (TTP), and median survival times (MSTs) when compared with 5-FU-LV alone. This combination represents a major advance in the treatment of metastatic colorectal cancer and should be considered the first-line treatment standard.

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Key Words: 5-fluorouracil; irinotecan; leucovorin; metastatic colorectal cancer.

INTRODUCTION

Colorectal cancer accounts for about 15% of all cancers in the United States, with approximately 130,200 new diagnoses and 56,300 deaths expected in 2000.¹ Colorectal cancer ranks third in mortality rates, behind rates for lung and prostate cancer in men and lung and breast cancer mortality rates in women.¹ If diagnosed in its early stages, colorectal cancer is highly curable with surgery alone. The

standard of care for patients with metastatic disease, however, is chemotherapy because surgery alone does not result in cure. Historically, fluorouracil (5-FU) has been the only cytotoxic agent effective in the treatment of advanced colorectal cancer; however, response rates (RRs) with 5-FU rarely, if ever, exceed 15%.² When 5-FU is combined with the biomodulator leucovorin (LV), RRs increase; however, survival rates are largely unaffected. Although 5-FU and LV are considered standard treatment for colorectal cancer, the optimal doses and schedules continue to be debated, clearly indicating that new therapies and therapeutic approaches are needed to improve existing treatment options. Irinotecan (Campto[®], Aventis Pharmaceuticals, Frankfurt, Germany; Camptosar[®], Pharmacia and Upjohn, Peapack, NJ, USA) is indicated for the treatment of metastatic colorectal cancer that has recurred or progressed following 5-FU-based

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chemotherapy. Recent data suggest that, when combined with 5-FU-LV, irinotecan produces superior RRs, time to tumor progression (TTP), and median survival times (MSTs) when compared with 5-FU-LV alone. Following a brief review of 5-FU-based therapies, the evidence supporting irinotecan as a new standard therapy for advanced colorectal cancer will be discussed.

5-FU-BASED THERAPY FOR ADVANCED COLORECTAL CANCER

Comparison of IV bolus and Infusional 5-FU

One possible reason for the low RRs associated with 5-FU is that the half-life is very short (8–14 minutes) and colorectal cancer growth is very slow, with only 3% of cells dividing at one time.^{2,3} Therefore, if 5-FU is administered as a bolus injection, the number of cells exposed to the drug is very small.⁴ Prolonging the infusion may increase the exposure of tumor cells in the S-phase of cell division.

Meta-analysis. A meta-analysis of six randomized trials evaluated bolus injection *versus* continuous intravenous infusion (CIV) in more than 1200 patients with advanced colorectal cancer (Table 1).⁵ Tumor RRs were significantly higher in patients receiving CIV 5-FU compared with patients receiving a bolus injection (22% *vs.* 14%, respectively; $P=0.0002$). Although no survival benefit was observed with CIV in any individual trial, the meta-analysis showed a significant advantage (MST, 12.1 *vs.* 11.3 months, respectively; $P=0.04$). One possible explanation for these results is that the cumulative dose of 5-FU was two or three times higher in the CIV group in most trials. However, the prolonged exposure of tumor cells to 5-FU may also have contributed to this positive outcome.

Comparison of 5-FU with 5-FU plus LV regimens

During the 1980s, several biochemical modulators (i.e., LV, interferon [IFN], levamisole) aimed at enhancing the

cytotoxic mechanism of action of 5-FU were investigated. The most persuasive evidence to support biochemical modulation of 5-FU cytotoxicity has been reported for LV, a compound that increases and prolongs the competitive inhibition of thymidylate synthase by stabilizing the tertiary complex formed by the active metabolite of 5-FU, fluorodeoxyuridine, and the enzyme.¹²

Meta-analysis. A June 1992 meta-analysis of 1381 patients in nine randomized trials compared 5-FU alone with 5-FU plus LV for the treatment of advanced colorectal cancer. The study used RR and survival rate as primary end points. Each of the nine trials fell into one of three broad categories based on the prescribed dose and administration schedule of 5-FU and LV (Table 2).¹³ The first group of trials added LV weekly to 5-FU (weekly regimens). The second group of trials administered 5-day courses of LV and 5-FU every 28 days (monthly regimens) and the third group of trials used a higher dose of 5-FU as the control group (high-dose [HD] 5-FU).

With a median follow-up of 13 months, objective tumor responses were observed in 11% of patients receiving 5-FU alone (15 complete responses [CRs], 49 partial responses [PRs]) compared with 23% of patients receiving 5-FU and LV (24 CRs, 157 PRs). No significant differences in survival times were observed between the two groups ($P=0.57$). The MST was 11 months for the 5-FU group and 11.5 months for the 5-FU-plus-LV group. These data confirm the results of individual trials, none of which reported a survival advantage.¹³

High-dose *vs.* low-dose LV plus 5-FU

Preclinical data suggested that the modulation of 5-FU may require higher concentrations of LV; therefore, Poon *et al.*²³ compared a high-dose (HD) (200 mg/m²/day) LV regimen with a low-dose (LD) (20 mg/m²/day) LV regimen. In this study, a total of 457 patients were randomized to one of three regimens: (1) 5-FU (370 mg/m²/day) plus HD LV; (2) 5-FU (425 mg/m²/day) plus LD LV; and (3) 5-FU plus HD methotrexate (MTX) with LV rescue. Both

Table 1. 5-FU CIV vs. 5-FU Bolus Injection

Trial	CIV 5-FU	5-FU bolus injection
ECOG ⁶	300 mg/m ² /day, without a rest period	500 mg/m ² , days 1–5, then 5-FU 600 mg/m ² /week, every 7 days
NCIC ⁷	350 mg/m ² /day, days 1–14, every 28 days	400–450 mg/m ² , days 1–5, every 28 days
MAOP ⁸	300 mg/m ² /day, without a rest period	500 mg/m ² , days 1–5, every 35 days
France ⁹	750 mg/m ² , days 1–7, every 21 days	500 mg/m ² , days 1–5, every 28 days
SWOG-1 ¹⁰	300 mg/m ² , days 1–28, every 35 days	500 mg/m ² , days 1–5, every 35 days
Jerusalem ¹¹	600 mg/m ² +LV 15 mg/6 hours PO, days 1–5, every 21 days	600 mg/m ² +LV 15 mg/6 hours PO, days 1–5, every 21 days
SWOG-2 ¹⁰	200 mg/m ² , days 1–28, every 35 days+LV 20 mg/m ² IV, every 7 days ×4, every 35 days	425 mg/m ² , days 1–5+LV 20 mg/m ² IVB, day 1, every 28 days × two cycles, then every 35 days

⁶The ECOG trial was a four-arm trial; however, the arms containing cisplatin were not included in the meta-analysis. [†]The SWOG trial was a seven-arm trial. Three arms were not included because they could not be directly compared with any other treatment arms. The remaining four arms were compared 2×2 because two contained LV (SWOG-2) and two did not (SWOG-1) reprinted with permission from the Meta-Analysis Group in Cancer.⁵

CIV=continuous intravenous infusion; ECOG=Eastern Cooperative Oncology Group; 5-FU=fluorouracil; IVB=intravenous bolus; LV=leucovorin; MAOP=Mid-Atlantic Oncology Program; NCIC=National Cancer Institute of Canada; SWOG=Southwest Oncology Group.

Table 2. 5-FU vs. 5-FU+LV in Colorectal Cancer Patients

Regimen	5-FU, mg/m ² /day	5-FU+LV, mg/m ² /day	Trial
Weekly LV	5-FU 500, days 1–5, every 28 days	5-FU 600, day 1+LV 500, day 1, every 7 days × 6, every 56 days or 5-FU 600, day 1+LV 25, day 1, every 7 days × 6, every 56 days	GITSG ¹⁴
	5-FU 450, days 1–5+5-FU 200, qod × 6, every 45 days	5-FU 600, day 1+LV 500 as a 2-hour infusion, day 1, every 7 days × 6, every 56 days	
	5-FU 600, day 1, every 7 days	5-FU 600, day 1+LV 200, day 1, every 7 days	Bologna ¹⁶
	5-FU 600, day 1, every 7 days	5-FU 600, day 1+LV 500, day 1, every 7 days	Genova ¹⁷
Monthly LV	5-FU 370, days 1–5, every 28 days	5-FU 370, days 1–5+LV 500, 24-hour infusion × 5.5 days, every 28 days	City of Hope ¹⁸
	5-FU 370, days 1–5, every 28 days	5-FU 370, days 1–5+LV 200, days 1–5, every 28 days	Toronto ¹⁹
	5-FU 400, days 1–5, every 28 days	5-FU 400, days 1–5+LV 200, days 1–5, every 28 days	GISCAD ²⁰
High-dose 5-FU	5-FU 12 mg/kg/day, days 1–5, then 15 mg/kg/day, day 1, every 7 days	5-FU 400, days 1–5+LV 200, days 1–5, every 28 days	NCOG ²¹
	5-FU 13.5 mg/kg/day, days 1–5, every 28 days	5-FU 400, days 1–5+LV 200, days 1–5, every 28 days	GOIRC ²²

5-FU=fluorouracil; GISCAD=Italian Group for the Study of Digestive Tract Cancer; GITSG=Gastrointestinal Tumor Study Group; GOIRC=Italian Oncology Group for Clinical Research; LV=leucovorin; NCOG=Northern California Oncology Group; RPCI=Roswell Park Cancer Institute; qod=every other day.

5-FU-LV regimens demonstrated a significant advantage over 5-FU-HD MTX in terms of RR (31% vs. 42% vs. 14%) and TTP ($P \geq 0.01$). MSTs were also higher in the 5-FU-LV groups (12.7 months) compared with the 5-FU-HD MTX group (8.4 months). Although the results of this study did not prove the superiority of LD over HD LV therapy, it did establish LV 20 mg/m² plus a bolus injection of 5-FU 425 mg/m²/day for 5 days every 4 weeks as the standard LD 5-FU-LV regimen (Mayo Clinic regimen).

COMPARISON OF 5-FU-LV REGIMENS

In 1992, de Gramont *et al.*²⁴ compared the following in 348 patients with advanced colorectal cancer: a bimonthly regimen of HD LV (200 mg/m² given as a 2-hour infusion) followed by a bolus injection of 5-FU (400 mg/m²) and a 22-hour CIV (5-FU 600 mg/m²) administered for 2 consecutive days every 2 weeks *versus* the Mayo Clinic regimen (LV 20 mg/m² plus a bolus injection of 5-FU 425 mg/m²/day × 5, every 4 weeks). Overall, patients receiving the bimonthly regimen had higher RRs (32.6% vs. 14.5%; $P = 0.0004$) and longer progression-free survival (PFS) times (27.6 vs. 22 weeks; $P = 0.0010$); however, MST, although longer in the bimonthly group, was not significantly different (62 vs. 56.8 weeks; $P = 0.067$). The bimonthly regimen also produced fewer grades 3 and 4 toxicities (11.1% vs. 23.9%; $P = 0.0004$), including diarrhea (2.9% vs. 7.3%), granulocytopenia (1.9% vs. 7.3%), and mucositis (1.9% vs. 7.3%). As a result of these findings, many European investigators consider the bimonthly, or de Gramont, regimen to be the standard 5-FU-HD-LV regimen, and it has become the comparator regimen in several studies

assessing new therapeutic agents or strategies for treatment of advanced colorectal cancer.²⁵

Additionally, the Association of Medical Oncology of the German Cancer Society (AIO) conducted a multicenter, randomized trial to evaluate whether weekly HD infusional 5-FU is effectively biomodulated by LV, IFN, or both.²⁶ Two-hundred thirty-six patients were randomized to one of three treatment groups: (1) 5-FU (2600 mg/m²/week CIV for 6 weeks followed by a 2-week rest period) plus HD LV (500 mg/m² IV over 2 hours); (2) 5-FU plus IFN (3×10^6 U SC, $3 \times$ per week); or (3) 5-FU plus HD LV plus IFN. The 5-FU dose was reduced to 2000 mg/m² in the 5-FU-LV-IFN group after toxicities were observed. Overall, RRs were significantly higher for patients receiving 5-FU-LV or 5-FU-LV-IFN compared with patients receiving 5-FU-IFN (Table 3). Additionally, median TTP and survival time were significantly longer in the 5-FU-LV treatment groups.²⁶

Although the primary objective of this study was to determine effective biomodulation of 5-FU, the role of weekly HD infusional 5-FU (the AIO regimen) in the treatment of advanced colorectal cancer was also defined.²⁶

Both HD and LD 5-FU-LV regimens are used in clinical practice. Currently, the Mayo Clinic regimen administered monthly is widely accepted as the standard LD regimen in the United States, whereas the de Gramont and AIO infusional regimens are widely accepted as treatment of advanced colorectal cancer in Europe.^{27,28} Despite the widespread use of these regimens, none has proved superior in terms of overall survival time (OST). Therefore, researchers have more recently focused on the efficacy of a topoisomerase I inhibitor that appears to prolong survival

Table 3. RR, TTP, and MST in Colorectal Cancer Patients Receiving 5-FU With or Without LV and/or IFN²⁶

	RR, %*	TTP, months [†]	MST, months [‡]
5-FU+LV (n=91)	44	7.1	16.2
5-FU+IFN (n=90)	18	3.9	12.7
5-FU+LV+IFN (n=49)	27	6.3	19.6

*RR with 5-FU+LV vs. 5-FU+IFN, $P < 0.05$; RR with 5-FU+LV vs. 5-FU+LV+IFN, statistically equivalent. [†]TTP with 5-FU+LV vs. 5-FU+IFN, $P = 0.005$; 5-FU+LV+IFN vs. 5-FU+IFN, $P = 0.02$; 5-FU+LV vs. 5-FU+LV+IFN, $P = 0.89$. [‡]MST with 5-FU+LV vs. 5-FU+IFN, $P = 0.02$; 5-FU+LV+IFN vs. 5-FU+IFN, $P < 0.05$; 5-FU+LV vs. 5-FU+LV+IFN, $P = 0.8$. 5-FU=fluorouracil; IFN=interferon; LV=leucovorin; MST=median survival time; RR=response rate; TTP=time to disease progression.

times in advanced colorectal cancer patients who have failed first-line therapy.

IRINOTECAN IN THE SECOND-LINE TREATMENT OF COLORECTAL CANCER

Topoisomerase I inhibitors are S-phase-specific agents that stabilize the covalent DNA-topoisomerase I complex, resulting in single-stranded DNA breaks.²⁹⁻³¹ Irinotecan is a topoisomerase I inhibitor approved in the United States and Europe for the treatment of metastatic colorectal cancer that has recurred or progressed following 5-FU-based chemotherapy. It was the first antineoplastic agent to receive accelerated approval from the US Food and Drug Administration (FDA), with approval, therefore, not based on the results of randomized, controlled clinical trials, but on consistent activity observed in phase II trials.

Results of two European phase III trials reported improved survival times in 5-FU-refractory colorectal cancer patients receiving irinotecan: one trial compared irinotecan with CIV 5-FU, the other compared irinotecan with supportive care.^{32,33} Both trials used irinotecan 300 to 350 mg/m² every 3 weeks. The trial comparing CIV 5-FU with irinotecan evaluated 256 patients who had failed to respond to first-line 5-FU or who had progressed following 5-FU therapy.³² Overall survival was the primary end point with RR, adverse events, and quality of life (QOL) being secondary end points. With a median follow-up of 15 months, OST was longer in the irinotecan group ($P = 0.035$). Both MSTs and 1-year survival rates were increased in the irinotecan group compared with the 5-FU group (10.8 vs. 8.5 months and 45% and 32%, respectively). PFS also favored the irinotecan group (4.2 vs. 2.9 months; $P = 0.03$). Although RR was not the primary end point of the study, it was evaluated and found to be higher for patients receiving irinotecan compared with 5-FU (16% vs. 5%, respectively). QOL was similar between the two groups.³²

Similarly, Cunningham *et al.*³³ randomized 279 patients with metastatic colorectal cancer refractory to 5-FU-LV to either irinotecan 300 to 350 mg/m² every 3 weeks with supportive care or supportive care alone. Again, overall

survival was the primary end point. With a median follow-up of 13 months, the MSTs were 9.2 and 6.5 months for irinotecan and best supportive care, respectively, whereas 1-year survival rates were 36.2% and 13.8%, respectively ($P = 0.0001$). QOL parameters also were improved in the irinotecan group as evidenced by survival without a decrease in performance status, survival without a weight loss of greater than 5%, and survival without pain.

Based on these two pivotal trials, irinotecan was approved as treatment of metastatic colorectal cancer that has failed or progressed following 5-FU-based therapy. The positive results observed in these studies, along with irinotecan's lack of cross-resistance with other chemotherapy agents and mechanism of action that differs from 5-FU, led to phase III trials evaluating the use of irinotecan in combination with 5-FU-LV as first-line treatment for advanced colorectal cancer.

IRINOTECAN IN THE FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER

Trials to determine maximally tolerated dose (MTD) of irinotecan plus 5-FU-LV

Vanhoefer *et al.*³⁴ conducted a phase I trial to determine the MTD of a weekly schedule of irinotecan, LV, and a 24-hour infusion of 5-FU as first-line treatment in advanced colorectal cancer. Twenty-five patients received fixed doses of irinotecan 80 mg/m² and LV 500 mg/m², with escalating doses of 5-FU ranging from 1.8 to 2.6 g/m². At these 5-FU doses, no dose-limiting toxicities were observed. In the final dose escalation step, the irinotecan dose was increased to 100 mg/m² and administered with LV 500 mg/m² and 5-FU 2.6 g/m². At this dose level, dose-limiting diarrhea occurred. Although tumor response was not the primary end point of this study, 16 of 25 patients (64%) achieved an objective response. These results indicate that the addition of irinotecan to weekly infusional 5-FU-LV (AIO regimen) is feasible and results in improved RRs. The recommended doses for further study were irinotecan 80 mg/m², LV 500 mg/m², and 5-FU 2.6 g/m² administered weekly for 6 weeks followed by 1 week of rest.

Similarly, the Southern Italy Cooperative Oncology Group conducted a phase I study in 31 patients of irinotecan plus 5-FU-LV given concurrently every 2 weeks.³⁵ The primary end point was the MTD of both 5-FU and irinotecan with a fixed dose of LV. The starting dose of irinotecan was 150 mg/m² followed by LV 250 mg/m² as a 2-hour infusion plus a starting dose of 5-FU 600 mg/m² administered as a bolus injection. No inpatient dose escalation was allowed; thus, patients were treated with the same doses until they achieved a major response or disease progression occurred. A total of six doses levels were evaluated with at least three patients treated per dose level. Dose level 5 (irinotecan 210 mg/m², LV 250 mg/m², 5-FU 950 mg/m²) was the MTD as evidenced by grade 4 neutropenia in four of six patients. Dose level 4 (irinotecan 175 mg/m², LV 250 mg/m², 5-FU 950 mg/m²) was

Investigational Arm (N=54)

Irinotecan 80 mg/m ²	LV 500 mg/m ²	5-FU CIV 2300 mg/m ²
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Control Arm (N=43)

LV 500 mg/m ²	5-FU CIV 2600 mg/m ²
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Figure 1. Treatment schedule: weekly. For both arms, treatment was administered on days 1, 8, 15, 22, 29, and 36; one cycle=six infusions (7 weeks). CIV=continuous intravenous infusion; 5-FU=fluorouracil; LV=leucovorin.

recommended for further phase II evaluation. Dose level 6 (irinotecan 200 mg/m², LV 250 mg/m², 5-FU 850 mg/m²), which produced acceptable toxicity, was also considered an appropriate regimen for further study. Although RR was not the primary end point of the study, 14 of 26 assessable patients responded, yielding a 54% RR. In addition, at the time of analysis, median failure-free survival time and OST were 42 and 55 weeks, respectively.

Other trials evaluating irinotecan combined with 5-FU-LV

In a phase III trial, Saltz *et al.*³⁶ randomized 666 previously untreated colorectal cancer patients to one of three treatment groups: (1) monthly 5-FU-LV (Mayo Clinic regimen); (2) weekly irinotecan (125 mg/m²) followed by LV (20 mg/m²) and 5-FU (500 mg/m²); and (3) weekly irinotecan alone. A comparison of irinotecan plus 5-FU-LV with 5-FU-LV revealed that overall RRs (49% *vs.* 27%; $P < 0.001$), median time to treatment failure (TTF) (5 *vs.* 3.8 months; $P < 0.05$), and percentage of patients with a TTF of more than 6 months (42% *vs.* 25%; $P < 0.01$) were superior in the group receiving the combination of irinotecan and 5-FU-LV. No survival comparisons were reported because median follow-up was only 7.1 months.

In March of 2000, Douillard *et al.*²⁸ published pivotal information further supporting the use of irinotecan in

Investigational Arm (N=145)

Irinotecan* 180 mg/m ²	LV 200 mg/m ² †	5-FU [†] IVB & 5-FU [†] CIV 400 mg/m ² 600 mg/m ²
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Control Arm (N=143)

LV 200 mg/m ² †	5-FU [†] IVB & 5-FU [†] CIV 400 mg/m ² 600 mg/m ²
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*Administered on day 1 only.

†5-FU-LV administered on days 1 and 2.

Figure 2. Treatment schedule: bimonthly. For both arms, one cycle=three infusions (6 weeks). CIV=continuous intravenous infusion; 5-FU=fluorouracil; IVB=intravenous bolus injection; LV=leucovorin.

Table 4. RDI in Irinotecan vs. No-Irinotecan Treatment Groups

Regimen	RDI
Irinotecan	
<i>Weekly</i>	
5-FU	0.81
Irinotecan	0.82
<i>Bimonthly</i>	
5-FU	0.92
Irinotecan	0.93
No irinotecan	
<i>Weekly</i>	
	0.90
<i>Bimonthly</i>	
	0.96

5-FU=fluorouracil; RDI=relative dose intensity.

combination with 5-FU-LV as first-line treatment for metastatic colorectal cancer. This European, multicenter, randomized trial of 385 previously untreated patients compared infusional 5-FU-LV with irinotecan ($n = 199$) or without irinotecan ($n = 188$). The study used either a weekly 5-FU-LV schedule (AIO regimen) or a bimonthly (de Gramont regimen) schedule that was chosen by the individual institution.^{24,26} Figures 1 and 2 show the treatment regimens.

Patient characteristics, such as age, weight loss of greater than 5%, gender, performance status, prior adjuvant therapy, and median number of organs involved, were equal in both treatment groups. The primary end point of this study was RR and several secondary end points were also evaluated, including TTP, TTF, OST, toxicity, and QOL. Treatment was administered until disease progression occurred, unacceptable toxicity developed, or consent was withdrawn.

Of 385 treated patients, 97 received the weekly AIO regimen and 288 received the bimonthly de Gramont regimen. The median duration of treatment was longer in

Table 5. Summary of Efficacy of Irinotecan vs. No-Irinotecan Treatment Groups

End point	5-FU-LV+ irinotecan ($n = 169$)	5-FU-LV alone ($n = 169$)	<i>P</i> value
RR	49%	31%	<0.001
Median TTP, months	6.7	4.4	<0.001
Median duration of response, months	9.3	8.8	0.08
Duration of response and stabilization, months	8.6	6.2	<0.001
Median TTF, months	5.3	3.8	0.0014
OST, months	17.4	14.1	0.031
Time to PS deterioration, months	11.2	9.9	0.046

5-FU=fluorouracil; LV=leucovorin; OST=overall survival time; PS=performance status; RR=response rate; TTF=time to treatment failure; TTP=time to disease progression.

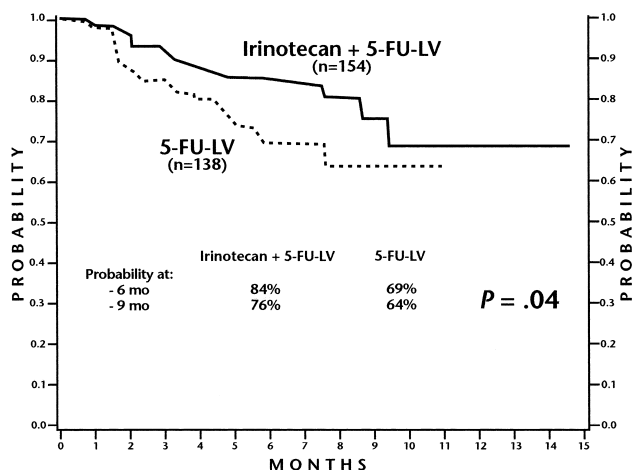


Figure 3. Time to 20% deterioration from baseline on QOL scale for irinotecan+5-FU-LV vs. 5-FU-LV.

the irinotecan group compared with the no-irinotecan group, regardless of regimen (24 vs. 21 weeks for the weekly regimen; 24.6 vs. 18 weeks for the bimonthly regimen). Relative dose intensity (RDI) was calculated in both groups and was reported to be higher in patients receiving the bimonthly regimen (Table 4).

With a median follow-up of 23 months, tumor response was higher and median duration of response, TTP, and MST were longer in the patients receiving irinotecan compared with patients receiving 5-FU-LV alone (Table 5). Additionally, the probability of survival was 82.1% at 9 months and 69.1% at 12 months for patients in the irinotecan group compared with 71.6% and 59.1%, respectively, for those in the no-irinotecan group. Using Cox's multivariate analysis, TTP, age and number of organs involved were significantly predictive of response. In patients < 58 years of age, the risk of progression increased by 28%, given that all other factors were equal. Furthermore, if ≥ 3 organs were involved, the risk of disease progression for a patient in the irinotecan group increased by approximately 56%, whereas the risk of disease progression in the no-irinotecan group was increased by approximately 69%.

The irinotecan group experienced more hematologic toxicities, such as grades 3 and 4 neutropenia, than did the no-irinotecan group, irrespective of weekly or bimonthly regimen ($P=0.001$). Grades 3 and 4 non-hematologic toxicities in the irinotecan and no-irinotecan groups consisted primarily of diarrhea (44% vs. 26%, respectively), nausea and vomiting (19% vs. 9%, respectively), and asthenia (7% vs. 0%, respectively). Dose reductions occurred more frequently in those receiving the weekly regimen compared with the bimonthly regimen and in the irinotecan group compared with the no-irinotecan group.

QOL was measured using a questionnaire, with the rate of return being similar between groups (irinotecan, 62%; no-irinotecan, 59%). Definitive deterioration in QOL occurred consistently later in the group receiving irinotecan compared with the no-irinotecan group (Figure 3).²⁸

CONCLUSIONS

Until recently, 5-FU-based therapy was the only treatment option for patients with advanced colorectal cancer. Although the addition of LV to 5-FU-based therapy increased RRs, survival rates were essentially unaltered. Researchers have therefore explored a promising topoisomerase I inhibitor, irinotecan, which appears to increase survival times and is currently FDA-approved for second-line treatment of colorectal cancer. Results of a pivotal study by Douillard *et al.* show that the combination of irinotecan and 5-FU-LV significantly increases RRs, significantly prolongs survival time and TTP, and prevents rapid deterioration of performance status. Based on these results, irinotecan plus 5-FU-LV represents a major advance in the management of metastatic colorectal cancer and should be regarded as the treatment of choice in this patient population.

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