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Promising New Drugs and Combinations

Irinotecan Plus Fluorouracil/Leucovorin for Metastatic Colorectal Cancer: A New Survival Standard

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ABSTRACT

Background. **Irinotecan is a topoisomerase I inhibitor that prolongs survival in patients with colorectal cancer refractory to fluorouracil (5-FU) and leucovorin (LV). This demonstrated activity of irinotecan as effective second-line therapy for colorectal cancer led to evaluation of combination irinotecan/5-FU/LV as first-line therapy for patients with metastatic disease. The results of two prospective phase III randomized, controlled, multicenter, multinational clinical trials in patients with previously untreated metastatic colorectal cancer served as the basis for U.S. and European approval of irinotecan/5-FU/LV for this indication. An overview of the findings of these two pivotal studies provides insights regarding the application of this new combination in clinical practice.**

Methods. **Patients were randomly assigned to receive 5-FU/LV, either alone, or with concurrent irinotecan. The study conducted primarily in North America (study 1), employed bolus 5-FU/LV schedules, while the study performed primarily in Europe (study 2), employed infusional 5-FU/LV regimens. Major endpoints included tumor response rate, time to tumor progression (TTP), overall survival, quality of life, and safety.**

Results. **In study 1, the respective confirmed response rates for irinotecan/5-FU/LV versus 5-FU/LV were 39% and 21% ($p < .001$); median TTPs were 7.0 months and 4.3 months, respectively ($p = .004$). In study 2, response rates for irinotecan/5-FU/LV versus 5-FU/LV alone were 35% and 22% ($p = .005$); median TTPs were 6.7 months and 4.4 months, respectively ($p < .001$). Survival time increased significantly with irinotecan/5-FU/LV versus 5-FU/LV alone in both studies (study 1: median 14.8 months versus 12.6 months, $p = .042$; study 2: median 17.4 months versus 14.1 months, $p = .032$). The combined analysis of the data from the two studies showed median survivals of 15.9 months versus 13.3 months, favoring the irinotecan-containing combinations (stratified-by-study $p = .003$). Patients in study 1 had a 36% lower risk of tumor progression and a 20% lower risk of death with the irinotecan combination than with 5-FU/LV alone; comparable risk reduction values in study 2 were 42% and 23%. While grade 3 diarrhea and vomiting were more common with irinotecan/5-FU/LV, grade 4 neutropenia, neutropenic fever, and mucositis were less common with irinotecan/5-FU/LV than with the Mayo Clinic 5-FU/LV regimen.**

Conclusion. **The combination of irinotecan/5-FU/LV is superior to 5-FU/LV alone as first-line therapy for patients with metastatic colorectal cancer, offering consistently improved tumor control and prolonged survival. Irinotecan-based combination therapy sets a new survival standard for the treatment of this life-threatening disease.**
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Introduction

Until recently, patients with colorectal cancer had few available chemotherapeutic options. In the absence of any more effective agent, 5-fluorouracil (5-FU) served as the mainstay of treatment for patients with advanced colorectal cancer for nearly 45 years [1]. A fluorinated pyrimidine, 5-FU acts by inhibiting thymidylate synthase, an enzyme necessary for the production of thymidine nucleotides required for DNA synthesis. 5-FU is usually given in combination with leucovorin (LV), a biomodulating agent that increases the binding of 5-FU to thymidylate synthase, thereby increasing the inhibition of DNA synthesis and enhancing the antitumor effect of 5-FU. This approach has increased response rates from 11% with 5-FU alone to 23% with 5-FU/LV but has provided no meaningful survival benefit (median survival 11.0 months with 5-FU alone versus 11.5 months with 5-FU/LV) [2]. Attempts to improve the efficacy of 5-FU by administration of protracted continuous infusions also showed a significant increase in response rate to 22%, but again, without improvement in survival beyond one year [3].

Irinotecan (CPT-11, CAMPTOSAR®, Pharmacia Corporation; Peapack, NJ; CAMPTO®, Aventis SA, Antony, France), a topoisomerase I inhibitor, offers a mechanism of action completely different from that of 5-FU in the treatment of colorectal cancer. Irinotecan and its metabolites bind to a complex of DNA and topoisomerase I (an enzyme required for unwinding of DNA during replication), inducing DNA strand breaks and consequent tumor cell death [4]. Irinotecan has shown antitumor activity in patients with colorectal cancer when administered alone as first-line therapy [5-8] or as second-line therapy after 5-FU failure [5, 7-9]. In two randomized phase III studies in patients who experienced failure of first-line 5-FU, irinotecan was compared with either best supportive care or with intensive 5-FU-based infusional therapy. Both studies showed a statistically significant survival benefit for patients treated with irinotecan [10, 11]. The activity of irinotecan against untreated and 5-FU-resistant colorectal cancer led to studies of this agent in combination with 5-FU/LV as first-line therapy for this disease.

Recently *Douillard et al.* and *Saltz et al.* reported the results of two studies conducted in parallel at a combined total of 154 institutions located primarily in North America and Europe [12, 13]. These studies evaluated irinotecan combined with either bolus (study 1: *Saltz*) or infusional 5-FU/LV (study 2: *Douillard*) in previously untreated patients with metastatic colorectal cancer. Both studies demonstrated statistically significant clinical benefits with the irinotecan/5-FU/LV combinations, including improved tumor control and prolonged survival. The major efficacy and safety results of these studies are summarized in this review.

Patients and Methods

Patient Demographics and Study Design

Both studies were large multinational, multicenter, randomized, open-label, controlled trials with similar inclusion and exclusion criteria. Male or female patients were eligible for enrollment if they were aged 18 years or older (but not more than 75 years for study 2), had a histologic diagnosis of colorectal cancer with unresectable measurable metastases and a performance status of 0-2, and had adequate hematologic, renal, and hepatic function. They could not have received prior chemotherapy for metastatic disease, or 5-FU-based adjuvant chemotherapy during the 12 months (study 1) or six months (study 2) preceding study entry. Patients who had previously undergone pelvic radiotherapy were excluded from study 1, but could enter study 2. All patients provided written informed consent before being enrolled.

In study 1, patients were prospectively stratified according to age (<65 or ≥65 years), time from initial diagnosis (<6 or ≥6 months), performance status (0 or 1-2), and prior adjuvant 5-FU-based therapy (yes or no). The patients were then randomized to one of three treatment regimens: irinotecan/bolus 5-FU/LV, bolus 5-FU/LV, or irinotecan alone. The treatment scheme for study 1 is depicted in Figure 1. In study 2, each study site chose one of two infusional regimens for administration of 5-FU/LV according to local clinical practice or preference, i.e., either

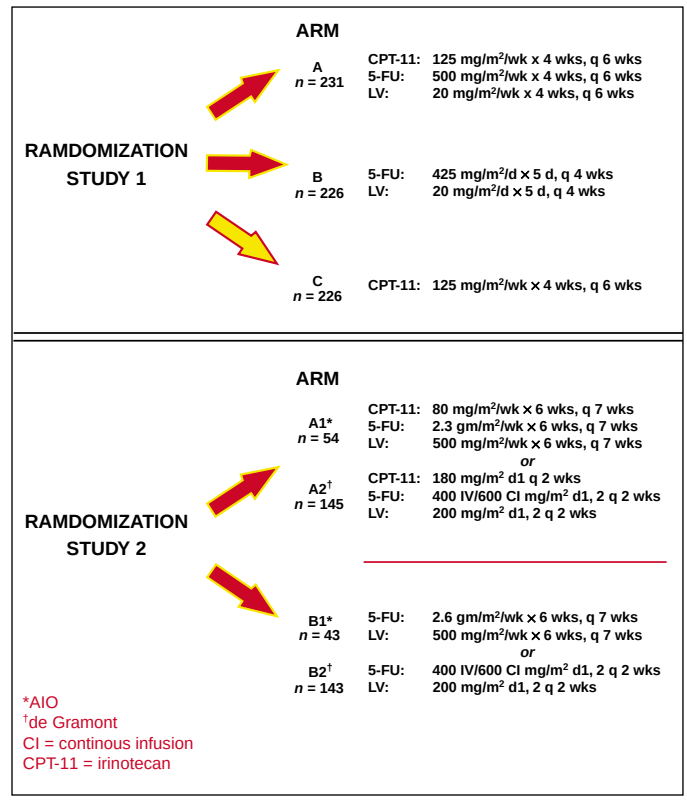

Figure 1. Treatment regimens for studies 1 and 2.

the once-weekly regimen of the Arbeitsgemeinschaft Internische Onkologie (AIO) cooperative German group for oncology [14] (designated A1 and B1 in Fig. 1), or the every-two-week regimen of *de Gramont* [15] (designated as A2 and B2 in Fig. 1). Once a site selected its preferred regimen (either AIO or *de Gramont*), patients at the site were randomized to receive that method of 5-FU/LV administration, with or without irinotecan. After initial treatment, doses in all treatment arms of both studies could be adjusted according to specified guidelines to accommodate individual patient tolerance to the study drugs [12, 13]. Treatment was continued until tumor progression, the occurrence of unacceptable toxicity, or the patient withdrew consent.

In both studies, atropine was provided for the treatment of cholinergic symptoms, and loperamide for treatment of delayed diarrhea. Antiemetic agents were administered as prophylaxis for nausea and/or vomiting. Granulocyte colony-stimulating factor could be given for prolonged neutropenia or infectious complications during neutropenic episodes.

Evaluations

The major clinical efficacy endpoints were similar in the two studies; both evaluated objective tumor response rates, time to tumor progression (TTP), and survival. In study 1, tumor measurements were obtained every six weeks until week 24, and then every 12 weeks until the end of study treatment. In study 2, tumor measurements were obtained after each chemotherapy cycle (every six to seven weeks) and at the end of study treatment. Objective tumor responses were confirmed at least four weeks after the first documentation of response. In both studies, quality of life (QOL) was measured at the start of each treatment cycle using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Following completion of study drug treatment, data were collected on post-study treatment for colorectal cancer and on survival.

Safety was evaluated in terms of adverse events, laboratory abnormalities, and deaths. Adverse-event assessments and complete blood counts were performed weekly, and chemistry studies were performed at the beginning of each chemotherapy cycle.

Statistical Methods

In study 1, a sample size of 220 patients per treatment arm was considered necessary to detect a 40% improvement in TTP (i.e., median TTP from five to seven months) in the irinotecan/5-FU/LV arm versus the 5-FU/LV arm with a power of 85% (two-tailed unstratified log-rank test, alpha of .05). In study 2, assuming a response rate of 35% for the 5-FU/LV arm and 50% for the irinotecan/5-FU/LV arm, a total of 338 evaluable patients (169 per arm) was considered necessary to provide 80% power to detect a significant difference in response rate (two-tailed chi-square test, alpha of .05). In the statistical comparison of irinotecan/5-FU/LV versus 5-FU/LV, results for patients who received regimens A1 and A2 were combined, as were results from patients treated with B1 and B2.

For both studies, time-to-event endpoints (e.g., duration of response, TTP, survival) were analyzed by Kaplan-Meier curves and unstratified log-rank tests. Response rates were compared using chi-square tests. The influence of stratification factors and other baseline characteristics on confirmed objective tumor response rates were assessed using multiple logistic regression modeling. Similarly, TTP and survival were assessed using Cox proportional hazard regression modeling. Changes in QOL subscale scores were assessed using analysis of variance for repeated measures. In study 1, worst changes from baseline were compared with Student's *t*-tests.

Irinotecan alone was included as a third treatment arm in study 1 only to document the efficacy and safety associated with its first-line single-agent use; consequently no hypotheses regarding its comparative efficacy were tested.

Table 1. Patient disposition

	Study 1			Study 2	
Patients	**Irinotecan 5-FU/LV**	**5-FU/LV**	**Irinotecan**	**Irinotecan 5-FU/LV**	**5-FU/LV**
	Arm A	**Arm B**	**Arm C**	**Arm A**	**Arm B**
Randomized (*n*)	231[a]	226[a]	226	199	188
Untreated (*n*)	4	8	4	1	1
Full-analysis (*n*)	—	—	—	198[a]	187[a]
Treated with a different arm (*n*)	2[b, c]	1[d]	1[e]	0	1[b]
As-treated (*n*)	225[f]	219[f]	223[f]	199[f]	186[f]

[a]Population analyzed for efficacy; [b]Randomized to irinotecan/5-FU/LV but received 5-FU/LV; [c]Randomized to irinotecan/5-FU/LV but received irinotecan alone; [d]Randomized to 5-FU/LV but received irinotecan alone; [e]Randomized to irinotecan alone but received 5-FU/LV; [f]Population analyzed for safety

Table 2. Baseline patient characteristics

Characteristic	Study 1			Study 2	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV	5-FU/LV
	Arm A (*n* = 231)	Arm B (*n* = 226)	Arm C (*n* = 226)	Arm A (*n* = 198)	Arm B (*n* = 187)
Age (years)					
Median	62	61	61	62	59
(Range)	(25-85)	(19-85)	(30-87)	(27-75)	(24-75)
Sex (%)[a]					
Male	65[b]	54	64	67[c]	53
Female	34	45	35	33	47
Performance Status (%)[a]					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Site, primary tumor (%)[a]					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
No. of involved organ sites (%)[a]					
1	64	66	62	62	63
2	26	23	28	23	28
>2	10	10	9	15	9
Prior adjuvant 5-FU (%)	11	8	10	26	24
Prior radiotherapy (%)					
Any	3	2	1	20	16
Pelvis/abdomen	2	1	1	–	–
Other sites	1	1	0	–	–
Baseline laboratory abnormalities (%)[d]					
CEA ≥100 ng/ml	40	39	37	35	32
Hemoglobin <11 g/dl	26	25	26	16	21
WBC ≥8 × 10^3/mm^3	52	53	51	47	38
LDH >UNL	60	56	53	43	45
Total bilirubin >UNL	7	4	10	7	7

Abbreviations: CEA = carcinoembryonic antigen; LDH = lactate dehydrogenase; UNL = upper normal limit; WBC = white blood cell count

[a]Data not available for some patients who were randomized but not treated; [b]p = .019 Arm A versus Arm B; [c]p = .006 Arm A versus Arm B; [d]Percentage based on patients with baseline data

Results

Patients

The studies enrolled a combined total of 1,070 patients treated at 154 multinational sites. A small number of patients were untreated or received a treatment regimen to which they were not originally randomized. Table 1 summarizes the populations for the two studies.

Baseline characteristics are summarized in Table 2. Across all treatment arms, the populations were generally divided similarly between patients with a performance status of 0 and those with a performance status of 1 or 2. However, the proportions of patients with a performance status of 2 in the irinotecan/5-FU/LV and 5-FU/LV groups of study 1 (15% and 13%, respectively) were about twice those of patients with a performance status of 2 in either arm of study 2 (7% and 8%, respectively).

Colonic primary tumors predominated in both studies, as might be expected given the epidemiology of the disease. The proportion of patients with rectal tumors in study 1 (~15%) was lower than that in study 2 (35% to 45%), presumably because patients with prior pelvic irradiation were excluded from study 1 but not from study 2. Because most patients had metastatic disease at initial diagnosis, relatively few patients (about 10% in study 1 and 25% in study 2) had received prior adjuvant 5-FU therapy.

With respect to baseline laboratory values, carcinoembryonic antigen (CEA) and total bilirubin levels were generally similar across the two studies. However, there were notably greater proportions of patients with a depressed hemoglobin level, elevated WBC, or abnormal serum lactate dehydrogenase (LDH) in study 1 than in study 2. These laboratory abnormalities are consistent with the performance

Table 3. Efficacy results

	Study 1			Study 2	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV	5-FU/LV
Efficacy endpoint	**Arm A (*n* = 231)**	**Arm B (*n* = 226)**	**Arm C (*n* = 226)**	**Arm A (*n* = 198)**	**Arm B (*n* = 187)**
Overall objective response rate (%)	50	28	29	49%	31%
	$p < .0001$			$p < .001$	
Confirmed tumor response rate (%)[a]	39	21	18	35	22
	$p < .0001$[b]			$p < .005$[b]	
CEA response rate (≥50% decrease) (%)	55	38	44	—	—
	$p < .001$			—	
Median TTP (months)	7.0	4.3	4.2	6.7	4.4
	$p = .004$[c]			$p < .001$[c]	
Median survival (months)	14.8	12.6	12.0	17.4	14.1
	$p = .042$[c]			$p = .032$[c]	

Abbreviations: CEA = carcinoembryonic antigen; TTP = time to tumor progression

[a]Confirmed ≥4 weeks after first evidence of objective response; [b]Chi-square test; [c]Unstratified log-rank test

status findings, possibly indicating greater tumor burden or tumor-related organ dysfunction among the patients in study 1.

Efficacy

Efficacy data for studies 1 and 2 are summarized in Table 3. Remarkable consistency between the studies was observed when examining the efficacy outcome measures.

Response Rates

In study 1, the overall response rate (response defined as shrinkage of measured tumors by ≥50% on at least one occasion) was significantly higher for patients treated with irinotecan/5-FU/LV than for those treated with 5-FU/LV (50% versus 28%, $p < .0001$); comparable rates were also significantly higher in study 2 (49% versus 31%, $p < .001$). The confirmed response rates (based on responses confirmed by imaging tests ≥4 weeks later) were also significantly ($p < .005$ to $p < .001$) and consistently higher among patients who received irinotecan/5-FU/LV compared with those who received 5-FU/LV in both studies (Table 3). The median duration of confirmed objective tumor response from time of randomization was about nine months across all treatment arms. Examination of confirmed response rates by subgroup analyses showed that, for every subgroup evaluated, including patients with poor performance status, extensive metastatic disease, prior adjuvant therapy, or abnormal baseline laboratory values, the response rate with irinotecan/5-FU/LV was approximately double that with 5-FU/LV alone [16].

CEA

Serum CEA was assessed systematically during study 1. CEA response (≥50% decrease from baseline in serum CEA during treatment) was evaluated in patients with elevated baseline CEA values and at least one CEA assessment while on treatment. The CEA response rate with irinotecan/5-FU/LV was substantially higher than with 5-FU/LV; this difference was significant ($p < .001$) (Table 3).

TTP

TTP was significantly longer in both studies for patients who received irinotecan/5-FU/LV than for those who received 5-FU/LV (study 1: median 7.0 months versus 4.3 months, $p = .004$; study 2: median 6.7 months versus 4.4 months, $p < .001$). As in the case of response rate, TTP was universally improved in all patient subgroups [16]. Kaplan-Meier TTP curves for both studies are shown in Figure 2.

Survival

Comparison of survival with irinotecan/5-FU/LV versus 5-FU/LV in study 1 showed a significant ($p = .042$) difference favoring the irinotecan combination (Table 3); at any given time on study, patients treated with irinotecan/5-FU/LV had a 19% reduction in the risk of death relative to those treated with 5-FU/LV alone (hazard ratio 0.81, 95% CI = 0.65-0.99). Similarly, in study 2, survival was significantly ($p = .032$) longer with irinotecan/5-FU/LV therapy than with 5-FU/LV; the risk of death at any time on study was decreased by 23% with the irinotecan combination relative to 5-FU/LV alone (hazard ratio 0.77, 95% CI = 0.60-0.98). The combined data from the two studies showed median survivals of 15.9 months for irinotecan/5-FU/LV versus 13.3 months for 5-FU/LV alone; a stratified-by-study analysis indicated a significant ($p = .003$) reduction in the risk of death at any time on study of 21% with the irinotecan/5-FU/LV arms relative to

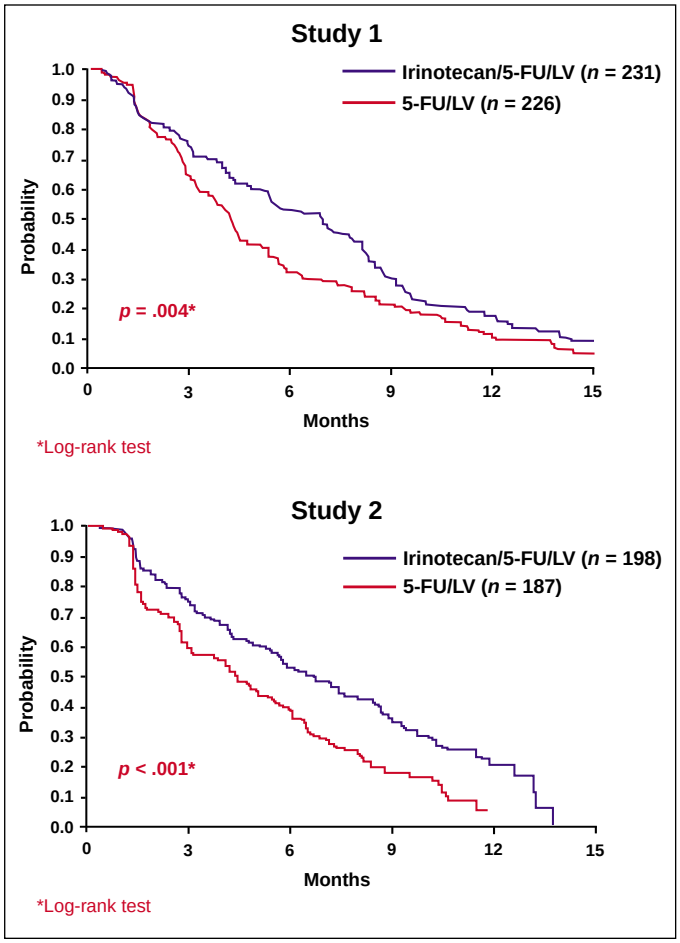

Figure 2. TTP—Kaplan-Meier estimates from two phase III studies.

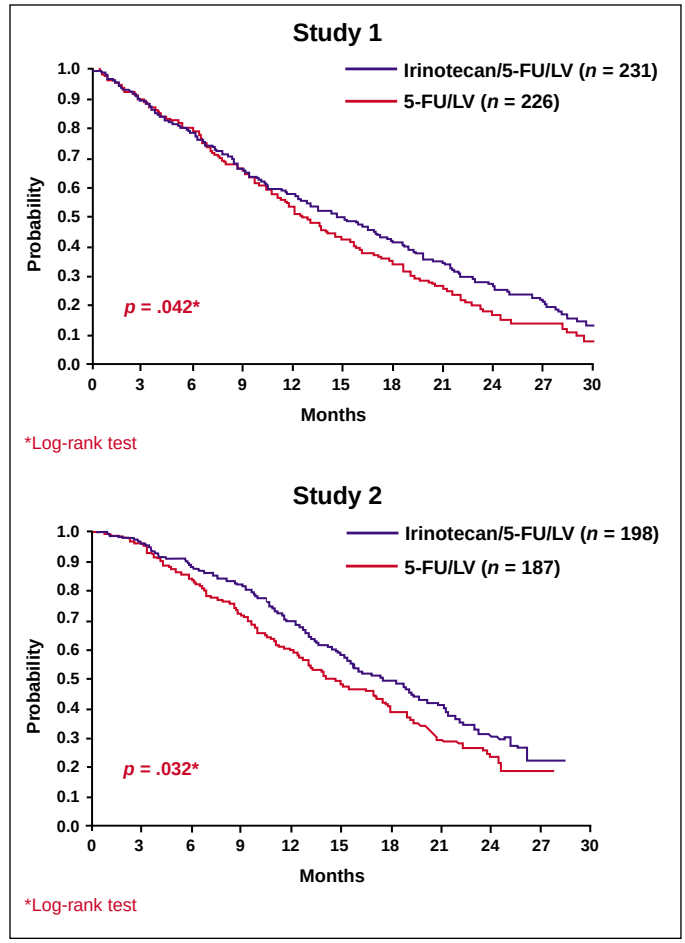

Figure 3. Survival—Kaplan-Meier estimates from two phase III studies.

the 5-FU/LV control arms (hazard ratio 0.67, 95% CI = 0.57-0.79) [17]. Kaplan-Meier survival curves for studies 1 and 2 are shown in Figure 3.

It is apparent that the irinotecan/5-FU/LV curve separates from the 5-FU/LV curve later in study 1 than in study 2. This finding may possibly be explained by the greater proportion of patients with performance status 2 in study 1; such patients generally had survival times <6 months with either therapy. If only patients with performance status 0-1 are considered, survival results for the irinotecan/5-FU/LV arms are quite similar (medians of 17.2 months and 17.4 months in the 195 patients of study 1 and the 185 patients of study 2, respectively) and continue to contrast with the 5-FU/LV arms (medians of 13.8 months and 15.5 months in the 195 patients of study 1 and the 173 patients of study 2, respectively).

Single-Agent Irinotecan Results

A single-agent irinotecan arm was included in study 1 only to document the activity of this agent as monotherapy. Efficacy results in this arm of the study appeared generally similar to those observed with 5-FU/LV alone (Table 3).

Post-Study Treatment

Over 90% of the patients had follow-up information regarding post-study anticancer therapy. In study 1, 52% of these patients in the irinotecan/5-FU/LV-treated arm received some form of second-line therapy, compared with 70% in the 5-FU/LV-treated arm. For 56% of the patients in the 5-FU/LV arm, this second-line regimen consisted of irinotecan as a single agent or in combination. In study 2, 49% of patients in the irinotecan/5-FU/LV arm received post-study therapy compared with 65% of those in the 5-FU/LV arm. In this study, 34% of the 5-FU/LV-treated patients given post-study chemotherapy received second-line irinotecan (Table 4).

Proportional Hazards Modeling

In study 1, Cox regression techniques were used to evaluate the effects of the study treatments on TTP and overall survival as influenced by the four predefined stratification factors

Table 4. Post-study therapy

	Study 1			Study 2	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV	5-FU/LV
Efficacy endpoint	**Arm A (*n* = 205)**	**Arm B (*n* = 203)[b]**	**Arm C (*n* = 195)**	**Arm A (*n* = 167)**	**Arm B (*n* = 171)[c]**
Total patients with post-study therapy[a]	52%	70%	79%	49%	65%
Irinotecan-based	1%	38%	3%	2%	28%
Irinotecan/5-FU-based	13%	18%	9%	4%	6%
5-FU-based	30%	10%	64%	32%	21%
Other therapy	8%	4%	3%	11%	10%

[a]Based on patients with follow-up information (approximately 90% of patients); [b]Altogether, 56% of patients in this arm ultimately received a second-line regimen containing irinotecan as a single agent or in combination; [c]Altogether, 34% of patients in this arm ultimately received a second-line regimen containing irinotecan as a single agent or in combination.

Table 5. Cox regression results

		TTP			Survival		
Factors	**Values**	**Hazard Ratio**	**95% CI**	***p***	**Hazard Ratio**	**95% CI**	***p***
Study 1							
Serum LDH	≤UNL versus >UNL	0.60	0.47-0.76	.0001	0.47	0.37-0.60	.0001
Performance status	0 versus ≥1	0.74	0.59-0.93	.0088	0.57	0.45-0.71	.0001
No. of organ sites	1 versus ≥2 sites	0.63	0.50-0.80	.0001	0.67	0.54-0.84	.0004
Bilirubin	≤UNL versus >UNL	0.56	0.35-0.89	.0132	0.55	0.35-0.86	.0051
WBC	<8 versus ≥8 × 10^3/mm^3	—	—	—	0.64	0.51-0.80	.0001
Hemoglobin	≥11 versus <11	0.74	0.58-0.95	.0157	—	—	—
Age	≥65 versus <65	0.78	0.63-0.98	.0315	—	—	—
Treatment	**Irinotecan/5-FU/LV versus 5-FU/LV**	**0.64**	**0.51-0.79**	**.0001**	**0.80**	**0.64-0.99**	**.0372**
Study 2							
Serum LDH	≤UNL versus >UNL	0.61	0.46-0.80	.0012	0.55	0.42-0.72	.0001
Performance status	0 versus ≥1	—	—	—	0.52	0.41-0.67	.0001
Time from metastatic diagnosis	≥1 mo versus <1 mo	0.62	0.48-0.80	.0003	0.63	0.49-0.82	.0005
No. of organ sites	1 versus ≥2 sites	0.71	0.55-0.91	.0070	0.73	0.57-0.94	.0127
Treatment	**Irinotecan/5-FU/LV versus 5-FU/LV**	**0.58**	**0.45-0.75**	**.0001**	**0.77**	**0.61-0.98**	**.0365**

Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; TTP = time to tumor progression; UNL = upper normal limit; WBC = white blood cell count

(age, performance status, time from initial diagnosis, and prior adjuvant therapy), as well as other baseline factors prospectively considered to have potential prognostic significance (e.g., number of involved organ sites, liver involvement, serum lactic dehydrogenase [LDH], hemoglobin level) [10, 11, 18-20]. As shown in Table 5, factors significantly predictive for both improved TTP and survival in study 1 were normal LDH, good performance status, fewer involved organ sites, and normal bilirubin. Higher hemoglobin level and normal WBC were significantly predictive of longer TTP and survival time, respectively. Surprisingly, older age also appeared to be significantly associated with a longer TTP.

Treatment with combination irinotecan/5-FU/LV remained a significant independent predictor of longer TTP ($p < .001$) and survival ($p = .037$) when other significant baseline patient characteristics were taken into account. In this adjusted analysis, irinotecan/5-FU/LV combination therapy was associated with a 36% lower risk of tumor progression and a 20% lower risk of death, than with 5-FU/LV therapy.

These findings were corroborated by application of the model developed in study 1 to the data from study 2 (Table 5). In this study, normal baseline serum LDH and fewer involved organs were found to be significant predictors for improved TTP and survival; better performance status was also significantly associated with longer survival. In this study, a longer time from diagnosis of metastatic disease to randomization was predictive for better outcomes with respect to both TTP and survival. As in study 1, treatment with irinotecan/5-FU/LV in study 2 remained a significant predictor of improved survival and was associated with a 42% lower risk of tumor progression and a 23% lower risk of death relative to treatment with 5-FU/LV when adjusted for baseline prognostic factors.

SAFETY

The most frequently occurring adverse effects noted in studies 1 and 2 are shown in Table 6. For study 2, this review focuses on the safety data from the FDA-approved *de Gramont* irinotecan/5-FU/LV regimen and the corresponding 5-FU/LV control. In both studies, approximately 23% of patients treated with the combination irinotecan/5-FU/LV regimens experienced grade 3-4 diarrhea compared with approximately 10% to 14% of patients receiving 5-FU/LV alone. This difference was primarily in the incidence of grade 3 diarrhea; grade 4 diarrhea was comparably infrequent in the treatment and control arms of the two trials; for example, in study 1, the incidence was 8% in the irinotecan/5-FU/LV arm and 7% in the 5-FU/LV arm. As expected, grade 3-4 vomiting was somewhat more common with irinotecan-based therapy but occurred in <10% of patients in any of the combination arms.

Of note, grade 3-4 mucositis was quite infrequent with irinotecan-based therapy, occurring in <4% of patients receiving combination therapies. By contrast, the Mayo Clinic

Table 6. Incidence of adverse events

	Study 1			Study 2	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV	5-FU/LV
Adverse event	**Arm A (*n* = 225)**	**Arm B (*n* = 219)**	**Arm C (*n* = 223)**	**Arm A (*n* = 145)[a]**	**Arm B (*n* = 143)[a]**
Diarrhea (%)					
Grade 3/4	23	13	31	14	6
Grade 3	15	6	18	10	4
Grade 4	8	7	13	4	2
Vomiting (%)					
Grade 3/4	10	4	12	4	2
Grade 3	5	3	6	3	1
Grade 4	4	1	6	1	1
Mucositis (%)					
Grade 3/4	2	17	2	4	3
Grade 3	2	15	2	4	3
Grade 4	0	2	0	0	0
Neutropenia (%)					
Grade 3/4	54	67	31	46	14
Grade 3	30	24	19	36	13
Grade 4	24	43	12	10	1
Neutropenic complications (%)					
Neutropenic fever	7	15	6	3	1
Neutropenic infection	2	0	2	2	0
Discontinuations due to adverse events and drug-related deaths (%)					
Discontinuations	8	6	12	6	1
Drug-related deaths	1	1	1	1	0

[a]*de Gramont* regimen only

schedule of 5-FU/LV used in the control arm of study 1 and commonly employed as first-line therapy in North America was associated with a much higher frequency of severe, grade 3-4 mucositis (17%).

For neutropenia, only grade 4 events are usually associated with clinical consequences. Of interest, the frequency of grade 4 neutropenia with combination irinotecan/5-FU/LV therapy (24%) in study 1 was essentially half that observed in patients receiving 5-FU/LV in the control group (43%) and proportionately fewer patients experienced neutropenic fever when contrasting irinotecan/5-FU/LV (7%) with 5-FU/LV (15%). In study 2, where schedules of chemotherapy administration were similar, grade 4 neutropenia was more frequently seen when irinotecan was added to 5-FU/LV (10%) than with 5-FU/LV alone (1%). The incidence of neutropenic fever was also higher in the irinotecan/5-FU/LV arm (5.0%) than in the 5-FU/LV arm (1%); however, these rates of neutropenic complications are quite low when contrasted with many other chemotherapy regimens [21].

Discontinuations due to adverse events were acceptably low across all arms of both studies. The incidence of treatment-related death ranged from 0% to 1% in all treatment groups.

QOL

The primary repeated measures analyses of variance of changes from baseline in QOL in both studies showed no significant differences between the treatment arms. In study 1, results were significantly better with irinotecan/5-FU/LV than with 5-FU/LV when comparing worst changes from baseline for the subscales of role functioning, fatigue, appetite loss, and pain [22]. In study 2, deterioration of performance status occurred later in patients treated with the irinotecan combination than in those treated with 5-FU/LV alone (median 11.2 months versus 9.9 months, $p = .046$).

Discussion

Attempts to improve outcome in patients with metastatic colorectal cancer with modified 5-FU-based regimens, while generally resulting in higher response rates, have failed to significantly improve survival [3, 4]. However, the results of recent studies of the topoisomerase I inhibitor irinotecan have improved the outlook for patients with this disease. In these studies, irinotecan was shown to improve survival, first as single-agent second-line therapy [10, 11], and now as a component of first-line treatment with 5-FU/LV [12, 13, 17].

The two phase III randomized multicenter, multinational, controlled studies reviewed here compared the efficacy and safety of new combinations of irinotecan/5-FU/LV to that of traditional regimens of 5-FU/LV given as first-line therapy of metastatic colorectal cancer. The studies were similar in that they enrolled analogous patient populations, evaluated similar efficacy and safety endpoints, and applied standardized methods of analysis. The trials were complementary in that they assessed the use of irinotecan in combination with two different methods of 5-FU/LV administration (bolus and infusional therapy). Study 1 compared a new combination of irinotecan/bolus 5-FU/LV with that of the Mayo Clinic regimen of bolus 5-FU/LV that had been most widely employed in North America. Study 2 symmetrically determined the therapeutic ratio associated with adding irinotecan to two different infusional 5-FU/LV regimens that were widely used in Europe. Because the comparator regimens have been commonly used in oncology practices worldwide, the two studies provide clinicians with insights into the efficacy and safety of the new combinations relative to familiar standards.

The efficacy results of the two studies were remarkably consistent and show that the combination of irinotecan with 5-FU provides patients with significant reductions in tumor size in conjunction with prolonged suppression of tumor growth. The confirmed objective response rates with the irinotecan/5-FU/LV arms (39% and 35%) were 1.5 to 2 times those in the 5-FU/LV arms (21% and 22%), and these differences were statistically significant. In studies 1 and 2, respectively, TTP was significantly improved with combination treatment (medians, 7.0 and 6.7 months) relative to treatment with 5-FU/LV alone (medians, 4.3 and 4.4 months). Assessment of response rates and TTP across demographic and disease-related subgroups showed improvements with irinotecan-based combination therapy in all prospectively defined subgroups [16]. These results indicate that irinotecan/5-FU/LV has the potential to offer better tumor control to all patients who are eligible for first-line combination chemotherapy.

The most important finding of the studies was that first-line irinotecan/5-FU/LV combination treatment provided a statistically significant survival advantage. It is particularly noteworthy that this advantage occurred even though most control patients received second-line irinotecan therapy after on-study failure of 5-FU/LV. These results suggest that early combination irinotecan/5-FU/LV may be superior to sequential administration of first-line 5-FU followed by second-line irinotecan. The combination therapy survival outcomes noted among patients with good performance status accentuate this observation [16]. Such findings were presaged by the results of a prior study in metastatic colorectal cancer in which early administration of chemotherapy before symptom development was compared with delayed treatment after symptom development; as in the current experience, early therapy in that study resulted in significantly better survival [23].

Cox regression modeling, which assessed treatment effect adjusted for significant prognostic factors, provided

further evidence that combination therapy with irinotecan/5-FU improves TTP and survival. This analysis indicated that irinotecan/5-FU/LV treatment resulted in an approximate 40% reduction in the relative risk of tumor progression and a 20% decrease in the relative risk of death.

In both studies, gastrointestinal toxicities were more common with combination treatment, but grade 4 diarrhea—largely defined by the need for hospitalization for supportive care—was infrequent (<8%). In study 1, grade 4 neutropenia, neutropenic fever, and mucositis were observed less often with weekly irinotecan/5-FU/LV than with Mayo Clinic bolus 5-FU/LV alone; data from other studies that compared weekly versus monthly 5-FU/LV therapy [24, 25] suggest that this reduced toxicity with combination therapy is most likely due to the differences in 5-FU/LV scheduling between the arms. In study 2, clinically relevant grade 3 and 4 events, e.g., vomiting, mucositis, and neutropenic fever, were infrequent with the *de Gramont* irinotecan/5-FU/LV regimen. The safety findings were supported by the results of the QOL analyses, which showed that administration of irinotecan in combination with 5-FU/LV did not result in significant worsening of QOL.

Attempts to improve outcomes in patients with metastatic colorectal cancer with the limited tools of 5-FU and LV have been the source of decades of frustration and disappointment. Irinotecan has now broken the barrier to improved survival, first as single-agent second-line therapy, and now as a component of first-line combination treatment. The studies discussed here are the first trials to document that the combination of a new agent with 5-FU/LV can safely benefit patients with metastatic colorectal cancer by inducing tumor shrinkage, extending tumor control, and significantly prolonging life without an impairment of QOL. The strength and consistency of the data from these large complementary studies led the FDA's Oncology Drug Advisory Committee (ODAC) to conclude that irinotecan/5-FU/LV should be the reference standard against which future first-line therapies for metastatic colorectal cancer are compared.

Given the positive findings in patients with metastatic disease, several trials in the U.S. and Europe are comparing irinotecan/5-FU/LV with 5-FU/LV as adjuvant therapy for patients with stage III colon cancer; it is hoped that the addition of irinotecan to 5-FU/LV will offer an increased opportunity for cure in patients with early-stage disease.

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