Irinotecan (CPT-11) combined with bolus 5-fluorouracil/ leucovorin (Saltz regimen) as first-line chemotherapy of patients with advanced colorectal cancer

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Concerns about the safety of irinotecan (CPT-11) plus bolus 5-fluorouracil (5-FU)/leucovorin (LV) (the so-called Saltz regimen) have been previously reported. This prospective, multicenter, non-randomized study evaluated the anti-tumoral effect and toxicity of the Saltz regimen as first-line chemotherapy of 130 patients with advanced colorectal cancer (CRC). The median numbers of treatment cycles and infusions received per patient were 3 and 12, respectively. Eight (6.1) and 37 patients (28.5%) showed complete and partial responses, respectively [overall response rate = 34.6% (95% confidence interval = 20.7–48.5%)]. After a median follow up period of 9 months, 70 patients had died. The median progression-free survival and overall survival were 6.78 (0.3–33.8) and 8.26 months (range 0.3–33.8), respectively. The combined CPT-11/5-FU/LV treatment was well tolerated and no toxic deaths were reported. The most common grade 3/4 hematological toxicity was neutropenia (28% of patients and 3% of infusions), but no febrile neutropenia was reported. Delayed diarrhea was the most reported grade 3/4 non-hematological toxicity (21% of patients and 2% of infusions). Other non-hematological toxicities showed very low incidences. During the study five patients died due to factors not associated with disease progression. We conclude that the Saltz regimen administered on an outpatient basis was safe and well tolerated in patients with advanced CRC. Close monitoring of external patients together with an early treatment of toxicity was found to be essential to prevent severe and potentially fatal gastrointestinal or thromboembolic events previously reported with this CPT-11 combined regimen. *Anti-Cancer Drugs* 17:89–94 © 2006 Lippincott Williams & Wilkins.

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Introduction

Irinotecan (CPT-11) has become an important component of the therapeutic armamentarium in the treatment of colorectal cancer (CRC). Two pivotal, controlled, randomized, multicenter phase III trials – one conducted in the USA and Canada [1], and one in Europe [2] – showed a higher anti-tumoral efficacy for CPT-11 combined with 5-fluorouracil (5-FU)/leucovorin (LV) compared to 5-FU/LV alone as first-line chemotherapy in patients with advanced, metastatic CRC [1,2].

Saltz *et al.* [1] evaluated CPT-11 125 mg/m^2 and bolus 5-FU 500 mg/m^2/LV 20 mg/m^2 weekly for 4 weeks on a 6-week cycle. Douillard *et al.* [2] evaluated CPT-11 180 mg/m^2 combined with 5-FU 400 mg/m^2 i.v. bolus and 600 mg/m^2 by 22-h infusion plus LV 200 mg/m^2 on days 1 and 2 (the so-called 'de Gramont regimen'). Both first-line weekly bolus [1] or biweekly infusional [2] 5-FU/LV combined with CPT-11 improved survival over 5-FU/LV [3] and CPT-11 plus 5-FU/LV was then recommended as reference first-line chemotherapy for metastatic CRC [3,4].

Some concerns were later raised however, on the safety of CPT-11 plus bolus 5-FU/LV. During a clinical trial by the External Data Monitoring Committee of the North Central Cancer Treatment Group, the schedule of Saltz *et al.* [1] was administered and a higher, unexpected number of deaths occurred within the first 60 days of study [5]. A high death incidence was also reported in another multicenter trial that evaluated CPT-11 plus bolus 5-FU/LV compared with 5-FU/LV as adjuvant therapy for CRC [5,6]. Enrollment was temporarily suspended in these two studies and a panel of experts recommended a more aggressive supportive therapy [6]. Nevertheless, few data have since been published on the

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Table 1 Dose modification guidelines for toxicity

	At the time of i.v. infusion	At any time
Hematological toxicity		
absolute neutrophil count (ANC)	$<1.5 \times 10^9$/l	$\leq 0.5 \times 10^9$/l or $\leq 1.0 \times 10^9$/l + fever/infection
platelet count	$<100 \times 10^9$/l	$\leq 20 \times 10^9$/l
Non-hematological toxicity[a]		
treatment-related diarrhea	grade >1	grade 3/4
mucositis	grade >1	grade 3/4[a]
Actions	postpone i.v. infusion 1 week until ANC $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, diarrhea grade ≤ 1 and mucositis grade ≤ 1	postpone i.v. infusion 1 week until ANC $\geq 1.5 \times 10^9$/l, platelet count $\geq 75 \times 10^9$/l, diarrhea grade ≤ 1 and mucositis grade ≤ 1
Next doses	complete dose	20% dose reduction; 40% in case of a new severe toxicity; another new severe toxicity would imply definitive treatment discontinuation

[a]Or other grade 3/4 toxicities. After 2 weeks of delayed treatment without recovering, the treatment had to be discontinued. No re-escalation of dose was allowed after reduction.

tolerance of this CPT-11/5-FU/LV schedule. The Saltz regimen is more familiar to US oncologists (European schedules are often based on infusional 5-FU), but some new studies on bolus 5-FU/LV plus CPT-11 have been conducted in Europe [7,8]. The aim of this study conducted in Spain was to evaluate the anti-tumoral effect and toxicity of CPT-11 plus bolus 5-FU/LV (Saltz regimen) as first-line chemotherapy for patients with advanced CRC treated following current outpatient clinical practice. This clinical practice includes recommendations by expert panels for a strict monitoring of patients and an aggressive treatment of severe toxicities.

Material and methods

Selection of patients

To be enrolled, patients had to be ≥ 18 years old, to have a histologically confirmed diagnosis of advanced CRC with bidimensionally measurable disease, a WHO performance status ≤ 2 and a life expectancy ≥ 3 months. The laboratory data requirements before inclusion in the study were the following: polymorphonuclear neutrophil (PMN) count $\geq 2000/mm^3$, platelet count $\geq 100\,000/mm^3$, Hb ≥ 10 g/dl, serum creatinine level $\leq 135\mu$mol/l, bilirubin level $< 1.25 \times$ upper normal level (UNL) and ASAT/ALAT $\leq 3 \times$ UNL. If liver metastases were present, the bilirubin level could be $< 1.5 \times$ UNL and ASAT/ALAT $\leq 5 \times$ UNL.

Exclusion criteria were as follows: previous chemotherapy except for adjuvant fluoropyrimidine therapy finished at least 6 months before the study; high risk of poor outcome due to concomitant non-malignant disease (inflammatory enteropathy, major organic failure, uncontrolled severe infection); metastases in the central nervous system or resectable hepatic metastases; non-measurable disease (e.g. ascites, peritoneal disease, pleural hemorrhage, pulmonary carcinomatous lymphangitis or diffuse hepatic affectation); bowel obstruction or sub-obstruction; extensive pelvic radiotherapy; previous cancer history; lactating, pregnant women or patients with reproductive potential not implementing adequate contraceptive measures.

The study was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided their written, informed consent according to the Ethical Committees of each involved center.

Chemotherapy regimen

On day 1, the patients were treated with CPT-11 125 mg/m^2 given as a 90-min i.v. infusion followed by LV 20 mg/m^2 i.v. bolus and 5-FU 500 mg/m^2 i.v. bolus (Saltz schedule). The drugs were administered weekly for 4 weeks and the cycle was repeated every 6 weeks. Those patients who responded or showed stable disease received a maximum of 6 cycles unless disease progression or unacceptable toxicity appeared or consent was withdrawn. Further chemotherapy cycles could be administered according to the investigator's judgment. The guidelines for dose modification of CPT-11 due to toxicity are shown in Table 1.

Concomitant medication

Prophylaxis with anti-emetic agents was allowed according to the investigator's criteria. Curative atropine (0.25 mg s.c.) was administered if cholinergic symptoms appeared after CPT-11 infusion. In these patients, prophylactic atropine was administered in subsequent cycles. Curative treatment of delayed diarrhea was recommended and consisted of 2 mg of loperamide every 2 h for 12 h after the last episode of diarrhea for a maximum of 48 h consecutively. If diarrhea persisted for more than 24 h, oral prophylactic anti-biotherapy was prescribed. If diarrhea persisted for more than 48 h, the patients were admitted to hospital for parenteral rehydration and loperamide was replaced by other treatments (e.g. octreotide). Patients with febrile neutropenia were hospitalized, and treated with anti-biotherapy (oral fluoroquinolones) and specific support. Preventive use of colony-stimulating growth factors was

not recommended. Other anti-neoplastic treatments were not allowed during the study. Analgesic radiotherapy of bone lesions was allowed only if unrelated to objective disease progression. Irradiated tumor sites however, were not used for the evaluation of response.

Assessment of response and toxicity

Pre-study evaluations included medical history and physical examination, tumor measurements by abdominal and pelvic computerized tomography, hematology and biochemistry tests, and other examinations as clinically indicated. All patients were evaluated before each CPT-11 infusion (including toxicity and hematology tests), before each treatment cycle (including physical examination, evaluation of performance status, toxicity and hematology, and biochemistry tests) and upon completion of the treatment schedule (at which time a complete revision was conducted).

Response to treatment was evaluated after a minimum of 3 cycles and classified according to WHO criteria [9]. Secondary efficacy endpoints were duration of response (time from patient response to disease progression), progression-free survival (PFS) and overall survival (calculated both from the start of the treatment until progression or death, respectively). All toxicities experienced during the study were recorded and graded according to the National Cancer Institute's (NCI) Common Toxicity Criteria [10]. All patients were evaluated for adverse events regardless of their relationship to the study drug. All adverse events were graded for severity before each treatment cycle.

Statistical analysis

Statistical analyses were performed using the SAS version 8.0 statistical package. Toxicity analyses were performed on patients who received at least one dose of study treatment (safety population). All efficacy analyses were conducted on the intent-to-treat (ITT) population. Kaplan–Meier estimations were used for the duration of response, PFS and overall survival. The adverse events and response rate were calculated by punctual estimation with a 95% confidence interval (95% CI).

Results

Patient and treatment characteristics

In total, 130 patients were prospectively included in 27 health centers from December 1999 to November 2000. Their baseline characteristics are listed in Table 2. All patients showed adenocarcinoma in colon (81 patients, 62%), rectum (44 patients, 34%) or both (five patients, 4%). The primary diagnosis at baseline of most tumors was Dukes D (55%) and C (29%). Most patients (96%) had a baseline WHO performance status of 0–1. The median number of metastatic sites was $n = 1$ and the liver was the organ most frequently affected (62%). Most patients (85.3%) had previously undergone surgery and 17 patients (13%) received prior pelvic radiotherapy.

Table 2 Patient and disease characteristics at baseline ($n = 130$)

Characteristic	*n*	%
Age (years) [median (range)]	64 (35–90)	
Gender		
male	82	63
female	48	37
WHO performance status		
0	62	47.7
1	62	47.7
2	6	4.6
Primary site		
colon	81	62
rectum	44	34
both	5	4
No. of involved organs		
1	92	71
>1	38	29
No. of metastatic sites		
1 site		
liver	61	47
lung	11	8.5
other	20	15.3
>1 site		
liver + lung	8	6.2
liver + other	17	13.1
lung + other	5	3.8
other	8	6.1
Prior treatment		
surgery	111	85.3
pelvic radiotherapy	17	13

A total of 1726 infusions and 431 cycles were administered. The median number of treatment cycles and infusions received per patient was $n = 3$ (1–6) and $n = 12$ (range 1–24), respectively. Dose was reduced in 19 cycles (4.4%), treatment was delayed in 79 cycles (18.3%), and both dose reduction and delay were used in 20 cycles (4.6%). The main reason reported for dose reduction per cycle was non-hematological toxicity, while treatment cycles were delayed mainly due to hematological toxicity. The median relative dose intensity was similar for the three agents: 0.68 for CPT-11, 0.68 for LV and 0.68 for 5-FU.

Anti-tumoral response, PFS and survival

Table 3 shows the overall objective response rate found in all patients evaluable for response. Eight (6.1) and 37 patients (28.5%) showed complete and partial responses, respectively. Therefore, the overall response rate was 34.6% (95% CI 20.7–48.5%). Stable disease was observed in 49 (37.7) and 26 patients (20%) progressed during study treatment. Ten patients were no evaluable for response (seven due to protocol violation previous to first evaluation and three due to use of different methods of response evaluation comparing to those used at baseline). Hence, the rate of tumor growth control was 72.3% (95% CI 63.3–81.4%) with a median follow-up period of 9 months. The median PFS and the median overall

survival were 6.78 (0.3–33.8) and 8.26 months (range 0.3–33.8), respectively.

Toxicity

The combined CPT-11/5-FU/LV treatment was well-tolerated (Table 4) and no toxic deaths were reported. The most common grade 3/4 hematological toxicity was neutropenia (28% of patients and 3% of infusions), but no febrile neutropenia was reported. Delayed diarrhea was the most reported grade 3/4 non-hematological toxicity (21% of patients and 2% of infusions) followed by nausea/vomiting (12% of patients and 1% of infusions). Other non-hematological toxicities showed very low incidences. During the study five patients died due to reasons not associated with disease progression (one each due to infection, pulmonary embolism, surgical complications, toxicity after starting second-line chemotherapy and unknown cause).

Discussion

We found the response rate here (34.6%) similar to the 39% reported by Saltz *et al.* [1]. Table 5 summarizes the main anti-tumoral efficacy and toxicity results reported in Saltz' study, as well as in other recent clinical trials that evaluated this combined CPT-11/5-FU/LV schedule as first-line chemotherapy for advanced CRC. These studies have shown similar response rates: 33 [7] and 35% [8], respectively. Saltz *et al.* [1] did not indicate the rate of patients showing stable disease in their pivotal phase III study. If we add the objective response rate to the stable disease rate, however, the value found here (72.3%) agrees with the data previously reported [7,8] and confirms that about three-quarters of treated patients should benefit in terms of tumor growth control with this combined CPT-11 plus modulated i.v. bolus 5-FU schedule.

Apart from the anti-tumoral response, one of the results that promoted the use of multiagent chemotherapy in advanced CRC was a prolongation of survival when CPT-11 was added to the standard 5-FU/LV chemotherapy [1,2]. A further combined analysis of the results of both trials on first-line weekly bolus [1] and biweekly infusional [2] 5-FU/LV combinations with CPT-11 confirmed this improvement in survival compared with 5-FU/LV alone [3]. The survival reported here (8.3 months) is however, the lowest found in studies using the Saltz schedule: range 13.0–15.2 months [1,7,8].

The pattern of toxicity reported here is consistent with that previously found in the study by Saltz *et al.* [1], as well as in later studies [7,8]. The main dose-limiting toxicities associated with the Saltz regimen are diarrhea and febrile neutropenia [1,11]. The incidence of grade 3/4 diarrhea (21.1% of patients) and neutropenia (28.1% of patients) agrees with the ranges of 18.0–22.7 and 7.0–53.8% previously reported for these toxicities, respectively [1,7,8]. Moreover, no cases of severe mucositis were found.

As commented above, the safety of the Saltz regimen was questioned in a recently published letter that linked the use of CPT-11 with a high rate of deaths in two NCI-sponsored trials [5]. This report led to suspension of the ongoing clinical trials. A extensive re-evaluation of mortality data was performed by an independent panel [6]. The investigators examined pre- and post-approval

Table 3 Response rate to treatment (ITT population, $n=130$)

	n	%	95% CI
Complete response	8	6.1	2.0–10.3
Partial response	37	28.5	20.6–36.3
Stable disease	49	37.7	29.2–46.1
Progressive disease	26	20	13.0–27.0
Overall response rate	45	34.6	20.7–48.5
Tumor control rate	94	72.3	63.3–81.4

Table 4 Grade 3/4 treatment-related toxicity (%)

Toxicity	Patient ($n=130$)	Cycle ($n=1726$)
Hematological		
anemia	3.1	0.3
neutropenia	28.1	3.2
thrombocytopenia	0.8	0.1
Non-hematological		
cholinergic syndrome	0.8	0.1
constipation	1.6	0.2
delayed diarrhea	21.1	2.0
fever	0.8	0.1
infection	3.1	0.2
nausea/vomiting	11.7	1.0

Table 5 Main results of anti-tumoral efficacy and toxicity found with combined CPT-11 and i.v. bolus 5-FU/LV (Saltz regimen) as first-line chemotherapy in advanced CRC

Reference, no. patients	Anti-tumoral efficacy			Toxicity grade 3/4 (% patients)		
	Response rate (%)	Tumor growth control rate (%)	Median survival (months)	Diarrhea	Mucositis	Neutropenia
Saltz *et al.* [1], $n=231$	39.0	ND	14.8	22.7	2.2	53.8
Bouzid *et al.*[7], $n=51$	33.0	74	15.2	18.0	6	30.0
Moehler *et al.* [8], $n=46$	35.0	75.0	13.0	22	0	7.0
Present study, $n=130$	34.6	72.3	8.3	21.1	0	28.1

ND = not described.

cooperative group studies in the USA and Europe, as well as community practice records. The population included not only patients receiving the Douillard and Saltz regimens, but also patients being treated with 5-FU/LV without CPT-11 (Mayo Clinic, Roswell Park and de Gramont regimens). The re-analysis not only confirmed the relative efficacy, but also established the inherent safety of irinotecan – the 60-day mortality rate associated with the Saltz regimen was statistically similar to that found with the Douillard regimen [12]. This independent panel found the observed increase in death rate attributable not to chemotherapy, but to lack of care in patient selection, monitoring and supportive care. Therefore, in December 2001 the Oncologic Drugs Action Committee of the USA re-approved the use of both the Saltz and Douillard regimens for first-line therapy of CRC. The CPT-11 package revision included new cautionary recommendations, such as that patients with a performance status greater than 2 are at higher risk to develop adverse events, that monitoring during treatment is essential as most fatalities (gastrointestinal and thromboembolic events) occurred during the first cycles or that patients with fever associated with neutropenia need adequate prompt supportive care, including the early use of oral fluoroquinolones [6]. All these recommendations, some of which (e.g. aggressive treatment of delayed diarrhea with loperamide) are frequently used in European investigations, were strictly followed in this clinical trial conducted on an outpatient basis [13].

Concerns about the safety of CPT-11 combined with bolus 5-FU/LV were mainly due to high early death rates caused by gastrointestinal events (i.e. a collection of symptoms consisting of diarrhea, abdominal cramping, nausea, vomiting and anorexia) and thromboembolic events reported in two US trials [6,14]. Further studies (including the present clinical trial) however, have shown an acceptable tolerability of the combined CPT-11 regimen based on that used in Saltz's study [8]. In agreement with this acceptable toxicity profile, in our study we did not find any toxic deaths or patients withdrawing from the study due to severe gastrointestinal or thromboembolic toxic events. Bouzid *et al.* found two deaths in 51 CRC patients treated with the Saltz regimen: one patient died due to septic shock and another patient died of hypokalemia plus hyponatremia. Moehler *et al.* found a non-fatal case of pulmonary embolism among 40 treated patients [7,8]. Another patient with pre-existing thrombosis on the iliac arteries died 12 days after starting treatment due to an unknown cause. Moreover, Moehlers' study showed for the first time that the Saltz regimen did not affect the quality of life of patients. In all these recent studies, grade 3/4 neutropenia was lower (7–30%) than the 53.8% reported by Saltz *et al.* [1].

CPT-11 was the first drug added to 5-FU/LV that made a substantial difference in terms of clinical benefit in the treatment for advanced CRC. Most studies have confirmed CPT-11 to be a key component of multidrug CRC chemotherapy. However, at the same time as some ongoing studies are evaluating the most suitable schedule for CPT-11 and 5-FU combination (e.g. bolus or continuous infusion, simultaneous or sequential schedule) [11,15], other new therapeutic agents are strongly emerging as therapy for advanced CRC (e.g. growth factor receptor antagonists like cetuximab or bevacizumab) [16,17]. Therefore, clarification of the characteristics of current combined chemotherapies is an indispensable step for the further development of better treatments for advanced CRC [13]. Early anecdotal evidence suggests that most episodes of diarrhea and febrile neutropenia reported with the Saltz regimen occur after week 3 in each cycle, particularly in later cycles [11]. In an attempt to improve the tolerability of the Saltz regimen, a modification of this schedule to once weekly for 2 weeks with repeated cycles every 21 days (the so-called 'day 1/day 8 schedule') instead of the usual once weekly for 4 consecutive weeks schedule repeated every 6 weeks has been studied [18]. The incidence of severe diarrhea (9% of patients) was reduced, but neutropenia (35% of patients) was slightly higher than the range found with the standard Saltz regimen in the present study and in other recent trials, i.e. 7–30% [7,8]. Nevertheless, dose intensities using this schedule were above 90% compared with the approximately 70% dose intensity recorded with the Saltz schedule [1].

In conclusion, CPT-11 combined with weekly bolus 5-FU/LV (Saltz regimen) and administered on an outpatient basis is safe and well tolerated in patients with advanced CRC. Close monitoring of external patients together with an early aggressive treatment of toxicity are essential to prevent severe and potentially fatal gastrointestinal or thromboembolic events previously found of concern when using this CPT-11 combined regimen. Therefore, the combination of the Saltz regimen with new anti-tumoral agents opens another field in the treatment of advanced CRC, in combination with strict monitoring and early, aggressive treatment of treatment-related toxicities.

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