Phase II Study of Irinotecan as First-Line Chemotherapy for Patients with Advanced Colorectal Carcinoma

José Luis Fírvida, M.D.[1]
Antonio Irigoyen, M.D.[2]
Sergio Vázquez-Estévez, M.D.[3]
Pilar Díz, M.D.[4]
Manuel Constenla, M.D.[5]
Joaquín Casal-Rubio, M.D.[6]
Manuel Valladares-Ayerbes, M.D.[7]
Javier Castellanos, M.D.[8]
Rubén Rodríguez, M.D.[1]
Miquel Balcells, M.D.[9]

[1] Complexo Hospitalario de Ourense, Ourense, Spain.

[2] Complexo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain.

[3] Hospital Xeral Calde, Lugo, Spain.

[4] Hospital Virgen Blanca, León, Spain.

[5] Hospital Montecelo de Pontevedra, Pontevedra, Spain.

[6] Hospital Meixoeiro, Vigo, Spain.

[7] Hospital Juan Canalejo, A Coruña, Spain

[8] Hospital Xeral Cíes, Vigo, Spain.

[9] Prasfarma, Barcelona, Spain.

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Address for reprints: Miquel Balcells, M.D., PRASFARMA, C/. del Pont Reixat, 5, 08960 Sant Just Desvern, Barcelona, Spain; Fax: 34-3-4802360; E-mail: mbalcells@prasfarma.com

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BACKGROUND. The objective of this multicenter, open-labeled, Phase II study performed in Spain was to assess the efficacy and safety of irinotecan (CPT-11) as first-line chemotherapy for patients suffering from advanced colorectal carcinoma (CRC).

METHODS. Patients with histologically proven CRC and at least one bidimensionally measurable lesion, ages 18–70 years, with a performance status ≤ 2, normal analytical values, and no prior chemotherapy or only adjuvant chemotherapy completed before study entry were selected. The treatment schedule was CPT-11 350 mg/m^2 intravenously administered once every 3 weeks. Both tumor response and toxicity were assessed using the World Health Organization and National Cancer Institute common toxicity criteria. Changes in performance status, weight, and symptoms also were measured.

RESULTS. Sixty-five patients (44 chemotherapy-naïve patients and 21 patients who completed prior adjuvant treatment) were enrolled. Of these, 24.7% of patients responded to the treatment, and 41.5% of patients had stable disease. Patients who had not received prior adjuvant chemotherapy had a lower rate of progression on therapy (27.3%) compared with those who had received prior adjuvant chemotherapy (42.9%). The median survival was 19.9 months (range, 0.3–29.3 months). No significant differences were found in the median survival between chemotherapy-naïve patients and patients who had received previous chemotherapy. Grade 3–4 diarrhea and neutropenia were the most frequent severe toxic events, which were observed in 23.1% and 30.8% of patients and in 5.9% and 10.9% of the cycles, respectively.

CONCLUSIONS. The current antitumor efficacy results show that 350 mg/m^2 of CPT-11 administered every 3 weeks is an active and feasible first-line chemotherapy regimen for patients with CRC. Finally, the overall safety data confirmed that CPT-11 is a well tolerated treatment. ***Cancer* 2001;91:704–11.**

KEYWORDS: irinotecan, first-line chemotherapy, colorectal carcinoma, safety profile.

Colorectal carcinoma (CRC) is one of the most common malignancies and is the second leading cause of cancer death.[1] This malignancy is curable by surgical treatment if it is diagnosed in its early stages. Overall, around 50% of patients with CRC can expect to be fully cured by surgery; this is accompanied by improvements in survival thanks to the use of adjuvant therapy. However, approximately 50% of all newly diagnosed patients will develop incurable metastatic disease either at the time of diagnosis or after surgery.[2] For patients with advanced CRC, palliative chemotherapy or best supportive care is currently the mainstay of treatment.[3,4]

Extensive clinical research has been conducted, but few effective

anticancer agents have become available for the first-line treatment of patients with advanced CRC. For the past 45 years, 5-fluorouracil (5-FU) has been the main treatment for patients with CRC. However, despite 5-FU therapy, most of these patients only survive for approximately 1 year after diagnosis. Historically, the response rates to 5-FU alone in patients with advanced CRC have been 15% or less, with a limited impact on patient outcome.[5]

Irinotecan, also known as CPT-11, has resulted in encouraging data in the treatment of patients with CRC.[4,6–8] Like its parent compound, camptothecin, CPT-11 exerts its cytotoxic mechanism by binding to topoisomerase I, a nuclear enzyme important for DNA replication and transcription. Colon carcinoma cells seem to express high levels of this enzyme, especially in patients with advanced disease, whereas cells in S-phase have enhanced sensitivity to topoisomerase I inhibitors.[9] CPT-11 has shown clinically relevant antitumoral activity with a less severe and more predictable side-effect profile than the topoisomerase I inhibitors studied previously.[10]

CPT-11 is now available in many countries as a single agent as second-line therapy for patients with metastatic CRC. The United States Federal Drug Administration (FDA) approved CPT-11 for the treatment of metastatic CRC in patients with recurrent or progressive disease after receiving 5-FU-based therapy. Several Phase I and II studies have been performed in Europe, Japan, and the United States; these studies have been reviewed extensively.[11–13] The broad spectrum of preclinical antitumor activity observed with CPT-11 was confirmed in the clinical setting.[14] Different studies have reported response rates ranging from 14% to 32%. When it is given as a single agent in first-line treatment, partial responses of 19–32% and minor responses of 12% were observed, confirming that CPT-11 is active in first-line therapy.[15,16]

Based on the results of Phase I studies in Europe,[17–20] a CPT-11 dose regimen of 350 mg/m^2 every 3 weeks was selected for European Phase II studies, because this schedule apparently showed the best compliance and tolerability and the highest dose intensity. The current Phase II clinical trial was designed as part of the clinical development of CPT-11 in Spain. This open, uncontrolled, multicenter, Phase II clinical trial had the primary endpoint of obtaining data on the efficacy and safety of CPT-11 during first-line chemotherapy in patients with advanced CRC, including overall survival.

MATERIALS AND METHODS

Selection of Patients

A total of eight oncology centers in the area of Galicia, Spain, participated in this study. The protocol for this study was approved by the Ethics Committees of all oncology centers and was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided their written, informed consent. The eligibility criteria included a diagnosis of metastatic or unresectable, locally advanced CRC; one or more bidimensionally measurable target lesions; age between 18 years and 70 years; life expectancy $\geq$ 3 months; and a World Health Organization (WHO) performance status of $\leq$ 2. An interval of at least 4 weeks must have elapsed since the last adjuvant treatment (6 weeks for mitomicyn, nitrosureas, or extensive radiotherapy).

Patients with the following criteria were not eligible: previous treatment with topoisomerase I inhibitors, previous treatment of metastatic disease with chemotherapy, previous cancer history (except for resolved cervical carcinoma or basal cutaneous carcinoma), high risk of poor outcome for concomitant nonmalignant disease (inflammatory enteropathy, uncontrolled severe infection, major organic failure), metastases in the central nervous system, bulky disease (involving $>$ 50% of the liver volume, $>$ 25% of the lung volume, or palpable abdominal mass), or unresolved bowel obstruction. Lactating women or potentially childbearing women also were excluded.

Pretreatment evaluation consisted of a history and physical examination (including assessment of body surface, WHO performance status, and tumor size), complete blood cell count and prothrombin time, carcinoembryonic antigen (CEA) determination, and a biochemical profile (lactic dehydrogenase, aspartate aminotransferase [AST] and alanine aminotransferase [ALT], alkaline phosphatase, bilirubin, albumin, and creatinine). Measurable disease was defined as the presence of a lesion that could be measured bidimensionally by appropriate morphologic examination or by using imaging techniques.

Specific requirements were provided by the protocol for liver metastases: single-target lesions had to measure $>$ 3 cm to be considered measurable; and, in patients with multiple lesions, more than one lesion had to measure $>$ 2 cm, and the global lesion had to be $<$ 50% of the liver volume. The laboratory data requirements for each patient before study entry were as follows: polymorphonuclear neutrophil (PMN) count $>$ 2000/mm^3, platelet count $>$ 100,000/mm^3, hemoglobin $>$ 10 g/dL, serum creatinine level $<$ 135 μmol/L, bilirubin level $<$ 1.25 $\times$ upper normal limit (N), AST and ALT levels $<$ 2.5 $\times$ N, and prothrombin time $>$ 50%, unless liver metastases were present, in which case, the bilirubin level could be $<$ 1.5 $\times$ N, and AST/ALT levels could be $<$ 5 $\times$ N.

Concomitant antitumoral therapy was prohibited,

with the exception of localized radiation therapy for analgesia of bone lesions. However, the irradiated target tumors were not considered for evaluation. Supportive care, defined as the best care available as judged by the attending physician and according to each center's institutional standards, was allowed with the following specifications: High dose corticosteroids were permitted only as antiemetic therapy. Curative treatment with antiemetic agents was allowed at all times. No prophylactic treatment was permitted for patients with early diarrhea; however, if severe cholinergic symptoms were observed during or after CPT-11 infusion, then atropine (0.25 mg subcutaneously) was recommended as curative treatment and prophylaxis for subsequent cycles. Specific guidelines for the curative treatment of patients with delayed diarrhea were provided; these recommended 2 mg of loperamide every 2 hours for 12 hours after the last loose stool and for a maximum of 48 consecutive hours.

Chemotherapy Regimen

All patients were treated with 350 mg/m^2 CPT-11 (CAMPTO®; Prasfarma SA, Sant Just Desvern, Barcelona, Spain; Rhone-Poulenc Rorer, Anthony, France) as a 90-minute intravenous infusion (diluted in 250 mL normal saline solution) every 3 weeks. Dose intensity was calculated in terms of the dose of CPT-11 administered per week as a function of body surface area and never exceeded a total dose of 700 mg. The patients had to receive at least three consecutive cycles before the first assessment of tumor response, except in the case of progressive disease or severe toxicity. The patients who responded or had stable disease after three treatment cycles could continue treatment for at least six cycles, provided there was no disease progression or excessive toxicity. If there was no evidence of a tumor response after six cycles, then these patients were withdrawn from the study.

Hematologic and biochemical tests were performed between cycles. To continue with the following cycle, the patients had to have a PMN count $> 1500/mm^3$, platelet count $> 100{,}000/mm^3$, serum creatinine level < 135 μmol/L, bilirubin level $< 1.25 \times$ initial value, AST/ALT levels $< 2.5 \times$ initial value, prothrombin time $> 50\%$, and absence of residual clinical toxicity, especially gastrointestinal toxicity (e.g., diarrhea). Otherwise, the next CPT-11 cycle was delayed for 1 or 2 weeks. If no recovery was observed after a delay of 2 weeks, then the patients were withdrawn from the study. For patients with Grade 4 neutropenia, the dose was reduced to 262 mg/m^2. The patients who still experienced the same toxicity after receiving 262 mg/m^2 were removed from the study. No further dose reductions were considered. In the event of severe diarrhea (Grade 3 or 4) persistent during 2 weeks, the patients were withdrawn from the study.

Follow-Up

The patients visited the investigator for assessment and treatment on Days 1 and 8 of the first cycle; before each subsequent cycle and after Cycles 3, 6, and 9. Clinical and laboratory tests were performed every month during the 3 months after the last CPT-11 infusion, except when toxicity prolonged poststudy observation.

Assessment of Response

The primary efficacy endpoint was the response rate. Tumor response was assessed every three treatment cycles. All patients who were withdrawn from the study before the third treatment cycle due to disease progression were classified as treatment failures.

The response to treatment was classified according to WHO criteria.[21] The secondary efficacy endpoints included the duration of response (calculated from the start of treatment to the time of disease progression), the time to disease progression, and survival (calculated from the start of treatment). An additional objective of the current study was to compare the response to therapy of chemotherapy-naïve patients with that of patients who received prior adjuvant therapy.

Assessment of Safety

All adverse events experienced during the study were recorded and graded according to the National Cancer Institute common toxicity criteria.[22] The patients were evaluated for adverse events regardless of their relationship with the study drug. All adverse events were recorded and graded for severity before each treatment cycle. The patients were evaluated monthly for at least 3 months after the last CPT-11 infusion to document any late adverse events.

Statistical Analysis

All statistical analyses were performed using the SAS software program (SAS Institute, Cary, NC). The minimum sample size was estimated as 41 patients, assuming an expected objective response of 17% (type I error, 0.01; type II error, 0.05; withdrawal rate, 30%). An efficacy analysis was performed according to the protocol. Mean, median, standard deviation, and minimum and maximum values were used to summarize continuous data. The qualitative variables were described according to their frequency. Survival curves were estimated using the Kaplan–Meier method. Comparisons between curves were made using a two-

TABLE 1
Summary of Demographic and Disease Characteristics of Enrolled Patients at Baseline

Characteristic	No.	%
No. of patients	65	100.0
Gender		
Male	39	60.0
Female	26	40.0
Age (yrs)		
Median	59.0	—
Range	27–70	—
ECOG PS[a]		
0	28	44.4
1	29	46.0
2	6	9.5
Primary site		
Colon	29	44.6
Rectum	36	55.4
Disease sites		
Liver	50	66.7
Lung	9	12.0
Other	16	21.3
No. of disease sites		
1	56	86.2
> 1	9	13.8
Previous treatment		
Surgery	64	98.4
Radiotherapy	11	16.9
Chemotherapy (adjuvant)	21	32.3

ECOG PS: Eastern Cooperative Oncology Group Performance Status.
[a] Data from two patients were missing.

tailed log rank test. The adverse events were calculated by punctual estimation with a 95% confidence interval.

RESULTS

Clinical Characteristics

Between October 1996 and November 1997, all eligible patients seen entered this study. The characteristics of these 65 patients are listed in Table 1. The WHO performance status was in the range of 0–1 for most of the patients (90.4%). All patients studied showed adenocarcinoma; 29 (44.6%) in the colon and 36 (55.4%) in the rectum. The median time from CRC diagnosis was 8.7 months, and the time from the first diagnosis of metastases was 1.2 months. Eighteen patients (27.7%) showed metastatic sites at the time the received a positive diagnosis of CRC. Sixty-four of 65 patients had previously undergone surgery. A total of 74 surgical interventions were recorded; 41 (55.4%) of them curative and 33 (44.6%) palliative. Eleven patients (16.9%) received prior palliative pelvis radiotherapy, and 21 patients (32.3%) received prior adjuvant chemotherapy (5-FU chemotherapy). The median time between completion of adjuvant chemotherapy and entry in the current study was 12 months. Tumor progression was clear and documented in 55.4% of patients. Twenty-nine patients (45.3%) showed increases in CEA levels during the 3 months previous to the study. The median CEA concentration at the time of inclusion was 20.35 ng/mL. Fifty-six patients (86.2%) had only one affected organ, and the liver was the most affected organ (66.7%). Three patients underwent hepatic metastectomy after finishing the study. The symptoms most frequently reported during the baseline visit were asthenia (40%), anorexia (21.5%), and pain (33.8%). Forty-three patients (66.2%) had other nontumoral diseases, and 38 patients (58.5%) received prior and concomitant nonantitumoral therapy.

Response to Treatment

A total of 384 cycles were administered during the study: The median number of treatment cycles received was 6. The median dose intensity was 100 mg/m^2 per week (range, 68–118 mg/m^2). Dose reductions were recorded for 15 patients (23.1%) and 23 cycles (5.9%). Almost half of these reductions were due to hematologic toxicity. The other half of the reductions were caused by adjustment of the dose to loss of body weight: This was assessed as dose reduction, although the planned intensity of dose (350 mg/m^2) was kept in all patients. Sixty-three patients were evaluable after Cycle 3, 43 patients were evaluable after Cycle 6, and 7 patients were evaluable after Cycle 9. Only one patient was evaluable at Cycles 12 and 15, after which, disease progression was detected.

Table 2 shows the overall response to CPT-11 treatment during the study. Sixty-four of 65 patients included in the study were evaluable for efficacy of the treatment: Toxicity prevented the evaluation of only 1 patient. The responses for the 64 patients were as follows: complete responses in 4 patients (6.2%) and partial responses in 12 patients (18.5%), with an overall response rate of 24.7% (95% confidence interval, 14.8–36.9). Three complete responses were localized in the liver, and one complete response was localized in the liver and the adrenal glands. Nine partial responses were localized in the liver; two were localized in the lung; and one was localized in the liver, spleen, and adrenal glands. Stable disease was observed in 27 patients (41.5%), which included two minor responses, and 21 patients (32.3%) experienced progressive disease. No significant difference was found between the response rate of chemotherapy-naïve patients (25.0%) and that of previously treated patients (23.8%). Nevertheless, all four complete responses occurred in the group of previously untreated patients. The median time to achieve an objective

TABLE 2
Overall Response Rate to Irinotecan Treatment in Spanish Patients with Advanced Colorectal Carcinoma

Patient status	Rate (%)
Response to treatment (all patients: n = 65 patients)	
Complete response	4 (6.2)
Partial response	12 (18.5)
Stable disease[a]	27 (41.5)
Progressive disease	21 (32.3)
Not evaluable	1 (1.5)
Prior adjuvant chemotherapy (n = 21 patients)	
Complete response	0 (0)
Partial response	5 (23.8)
Stable disease[a]	7 (33.3)
Progressive disease	9 (42.9)
No prior adjuvant chemotherapy (n = 44 patients)	
Complete response	4 (9.1)
Partial response	7 (15.9)
Stable disease[a]	20 (45.5)
Progressive disease	12 (27.3)
Not evaluable	1 (2.3)

[a] Stable disease includes both minor response and stable disease.

response (the sum of complete responses and partial responses) was 3.7 months (range, 1.6–6.7 months), and the median duration of the response was 9.0 months (range, 3.8–25.8 months). The clinical benefit rate, i.e., the control of tumor growth shown by the total amount of patients responding to treatment and patients showing stable disease, was 66.2%.

Time to Disease Progression

The median time to disease progression was 6.4 months (range, 0.7–25.8 months). The time to disease progression was > 3 months in 72% of patients, > 6 months in 53% of patients, and > 9 months in 28% of patients. The median time to disease progression was the same for chemotherapy-naïve patients and for patients who had received previous chemotherapy (Fig. 1).

Survival

The median survival was 19.9 months (range, 0.3–29.3 months). The median survival was 19.6 months for chemotherapy-naïve patients and 20.2 months for patients who had received previous chemotherapy. No significant differences in median survival were found between chemotherapy-naïve patients and previously treated patients (Fig. 2). The survival for 90.6% of the patients was > 6 months, whereas it was > 9 months in 81.3% of patients.

Safety

The administration of CPT-11 was associated with an early cholinergic-like syndrome that occurred during

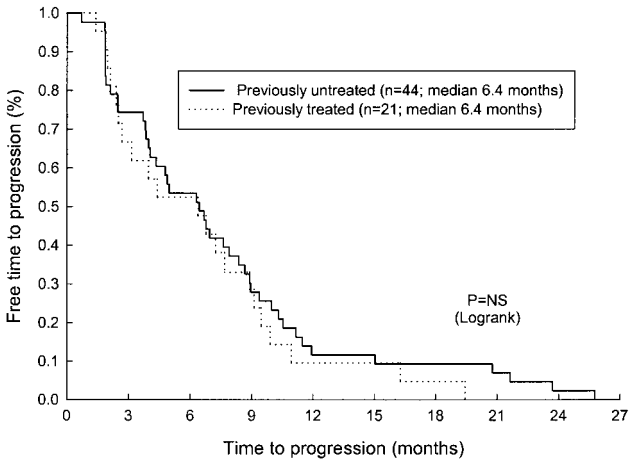

FIGURE 1. The time to disease progression for untreated patients (n = 44) and previously treated patients (n = 21) with advanced colorectal carcinoma. NS: not significant.

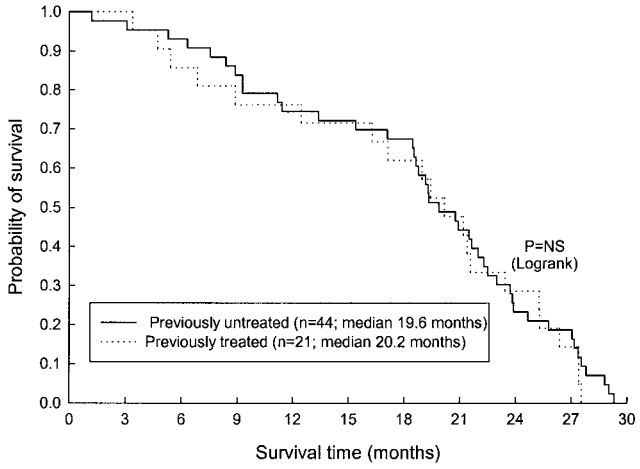

FIGURE 2. Survival curves for untreated patients (n = 44) and previously treated patients (n = 21) with advanced colorectal carcinoma. NS: not significant.

or immediately after infusion in 64.7% of patients and in 19.5% of cycles. The most frequent symptoms of this syndrome were nausea and emesis (50.9%), diaphoresis (40.0%), abdominal cramps (20.0%), early diarrhea (18.2%), and salivation (17.6%). These toxicities usually were mild to moderate in severity and short in duration: 56% of nausea was classified as WHO Grade 1, 72.7% of diaphoresis was classified as mild, 90.9% of abdominal cramps was classified as mild, 78.6% of early diarrhea was classified as WHO Grade 1, and 58.6% of salivation was mild. Other, less frequent symptoms included malaise (6.7%), lacrimation (6.7%), and visual disturbances (1.2%). Only 2.4% of the patients with nausea and emesis discontinued CPT-11 treatment for this reason, but most of them (78.3%) recov-

TABLE 3
Incidence of Grade 3–4 Toxicity Possibly or Probably Related to Irinotecan Administration in Spanish Patients with Advanced Colorectal Carcinoma

Toxicity	No. (%) per patient (n = 65 patients)	No. (%) per cycle (n = 384 cycles)
Diarrhea	15 (23.1)	23 (5.9)
Alopecia	12 (18.5)	37 (9.6)
Nausea and emesis	8 (12.3)	11 (2.9)
Asthenia	5 (7.7)	8 (2.1)
Neutropenia	20 (30.8)	42 (10.9)
Infection	2 (3.1)	2 (0.5)
Neurologic disorders	1 (1.5)	1 (0.3)
Fever	1 (1.5)	1 (0.3)

ered shortly thereafter. No patients with early diarrhea stopped the treatment, and 80% of these patients showed a rapid recovery.

Table 3 lists the overall incidence of Grade 3–4 toxicity according to the number of patients and cycles affected. The main toxicities were gastrointestinal and hematologic. Diarrhea was the most relevant toxicity found (83.1% of patients and 34.4% of the cycles). Nevertheless, Grade 3–4 diarrhea appeared in 23.1% of patients and in 5.9% of cycles. Of all episodes of severe diarrhea, 90.9% were treated with loperamide. Of all cycles in which diarrhea occurred, 20.5% required the patient to stay at home, and 4.7% led to hospitalization. Overall, 9 patients (13.8%) and 11 cycles (2.9%) required hospitalization due to toxicity, mainly diarrhea and infection.

Twenty patients (30.8%) and 42 cycles (10.9%) showed Grade 3 or 4 neutropenia. Febrile neutropenia appeared in one patient (1.5%) and one cycle (0.26%). Thirty-four patients (52.3%) showed diarrhea and neutropenia during the same cycle; 27.6% showed Grade 3 or 4 neutropenia, and only 3 patients (4.6%) experienced fever. One patient died during the study due to renal failure while suffering from concomitant neutropenia. Both effects were attributed to the study medication.

Four patients (6.2%) showed reversible changes in hemoglobin concentration, 2 patients (3.1%) showed reversible changes in platelet count, 7 patients (10.8%) showed reversible changes in white blood cell count, and 20 patients (30.8%) showed reversible changes in neutrophil count. Other common toxicities were alopecia, nausea and emesis, and asthenia. Nine patients showed an infection that was related to the medication in three patients and was considered to be severe in one patient. In one patient, medication was reduced, and, in another patient, it was interrupted. No serious pulmonary toxicity was observed.

Liver function impairment was reported in 15.4% of patients; this was related to treatment in 75.0% of patients and to the tumor in 12.5% of patients. Kidney function impairment was reported in 9.2% of patients; this was related to treatment in 42.9% of patients and to concomitant pathologies in 28.6% of patients.

DISCUSSION

This open-label, multicenter study assessed the clinical usefulness of CPT-11 administered once every 3 weeks at a dose of 350 mg/m^2 over a period of 90 minutes to Spanish patients with advanced CRC, some of whom previously had been untreated with chemotherapy. The main efficacy results found are comparable to those found in previous clinical trials and show that, at the dose studied here, CPT-11 is an effective treatment: 24.7% of patients responded to CPT-11 treatment, and 41.5% of patients showed stable disease. This high rate of disease stabilization is similar to that found by others.[23] The median time to disease progression was 6.4 months; this value is clinically significant in terms of tumor growth control in patients with rapid progression documented at study entry.

The data found here show that previously untreated patients were more likely to benefit from CPT-11 treatment compared with patients who received prior adjuvant therapy. The largest trial on a similar population, which was performed with 178 French patients, showed lower response rates in chemotherapy-naïve patients (18.8%) and in patients who were treated previously with a 5-FU-based regimen (17.7%).[2] However, studies conducted in Japan and the United States with weekly or intermittent regimens and CPT-11 doses of 100–150 mg/m^2 reported similar response rates: 15–32% in chemotherapy-naïve patients and 22–25% in pretreated patients.[6,7] Moreover, the overall response rate to CPT-11 in CRC patients as a first-line agent ranged from 18.8% to 32.0%, which is similar to the activity of currently used 5-FU-based regimens. The more significant outcome of these trials was the response rate in patients who were treated previously with chemotherapy. In this population, CPT-11 produced objective response rates of 14–23%, which may indicate a lack of cross resistance with 5-FU. This was a relevant finding, because patients usually react poorly to second-line treatments.

The median duration of response found in this study was 9.0 months for patients showing the best response to the treatment, but this decreased to 7.7 months for patients with minor response. The current results are in accordance with those of previous Phase II colorectal trials in Europe and the United States in

which the median duration of the response to CPT-11 ranged from 6 months to 9.1 months.[24]

The median survival measured in the current study compares favorably with that found in previous studies. Our patients showed a survival of 19.9 months, whereas the median survival values were 8.7 months in the American trials and 9.5–10.6 months in the European studies. One study on a combined therapy of alternate CPT-11 cycles with 5-FU showed a median survival (16 months) similar to that found here in CRC patients who were treated with CPT-11 only.[25] The survival of untreated patients and that of treated patients were similar. In the United States, the median survival of previously chemotherapy-treated patients was 8.3 months compared with 9.5–10.0 months in Europe. Chemotherapy-naïve patients showed an 11.8-month median survival in the United States[26] and a 12.0-month median survival in Europe.[1] The median survival is significant clinically in patients with metastatic CRC, particularly when 5-FU therapy has failed.[23] An analysis of the relationship between tumor response and survival in advanced CRC chemotherapy has shown that any degree of objective tumor response that lasts for 4 months is associated with a definite survival advantage.[27] The survival advantage conferred by stable disease was almost as great as that associated with partial response.

Special care must be taken when considering optimum doses of CPT-11:[28,29] almost 80% of the patients studied did not need dose reduction, suggesting that the starting dose was appropriate.[23] The safety profile found in this study for CPT-11 was acceptable, and the toxicity associated with CPT-11 treatment was manageable and anticipated: Only one death was attributed to effects related to CPT-11. The toxicity found is in accordance with that expected from this therapy: diarrhea, nausea and emesis, and neutropenia are the clinically most important adverse effects associated with CPT-11 therapy that may require dosage modifications.[28] The current study paid special attention to delayed onset diarrhea: Diarrhea is the dose limiting toxicity for CPT-11 and also is the cause of most hospitalizations and withdrawals from the treatment with CPT-11.[28] The mechanism by which delayed diarrhea associated with CPT-11 develops is uncertain. CPT-11-induced diarrhea differs from 5-FU-associated diarrhea, which is the result of generalized mucositis, in that it is not typically associated with a visible disruption of the colon mucosa or with changes in the colon bacterial microflora in humans.[30] Accordingly, only 7.7% of patients showed mild-to-moderate mucositis. The incidence of treatment-related Grade 3–4 delayed diarrhea with CPT-11 (23.1%) was similar or lower than that reported in previous studies.[2,23,31,32] Only 4.7% of the patients with diarrhea were hospitalized, and early treatment with loperamide reduced the severity of diarrhea. In general, the concomitant treatments used to reduce diarrhea or other early symptoms (i.e., loperamide, atropine) were effective in controlling adverse events. Finally, Grade 3–4 neutropenia was found in 30.8% of patients, and Grade 3–4 nausea and emesis was found in 9.0% of the patients: This is similar to the data reported in previous studies.[31]

In conclusion, the current study confirmed the efficacy and safety results found in other previous studies with 350 mg/m^2 CPT-11 administered once every 3 weeks in patients with CRC. More than 50% of the patients with CRC, with or without previous adjuvant chemotherapy, are likely to benefit in terms of tumor growth control. Moreover, the additional information from the safety profile of CPT-11 provided by the current study may contribute to improve the medical management of patients who undergo this chemotherapy regimen. Much remains to be learned about CPT-11. Because it was the first antineoplastic agent to undergo an accelerated review process for FDA approval, the data from Phase III, randomized, comparative controlled clinical trials were not available before approval. The drug was approved based on its consistent activity in reducing tumor-related symptoms. However, the impact of the drug on patient survival has been unknown until recently. The data collected from clinical studies worldwide show that CPT-11 represents a significant step forward in the treatment of patients with CRC, which is a particularly chemoresistant disease. We believe that further assessment of CPT-11 as first-line chemotherapy for patients with CRC is needed. Any factors that may predict the response to and toxicity from CPT-11 should be identified in the clinical research that currently is under way.

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