A phase II study of irinotecan, high-dose 24-h continuous intravenous infusion of floxuridine and leucovorin (IFLUX) for advanced, previously untreated colorectal cancer

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Our objectives were to determine response rate, time to progression, overall survival and tolerability of novel combination chemotherapy, consisting of irinotecan, high-dose 24-h continuous intravenous infusion of floxuridine and leucovorin in advanced previously untreated colorectal cancer. Thirty-eight patients with advanced colorectal cancer were treated at Sylvester Comprehensive Cancer Center, University of Miami, from 2000 to 2004, and received weekly intravenous infusion of irinotecan at 110 mg/m^2 with a combination of 120 mg/kg floxuridine and 500 mg/m^2 leucovorin administered as a 24-h continuous intravenous infusion. The treatment cycle consisted of 4 weeks of consecutive therapy followed by 2 weeks of rest. Five (13%) patients achieved complete response, 10 (26%) patients achieved partial response, 17 (45%) patients attained stable disease and six (16%) patients progressed. The overall response rate was 39% in this study. This chemotherapy regiment was well tolerated; the most common grade 3 toxicities were neutropenia (16%), anemia (16%), vomiting (24%), diarrhea (16%), and hand-and-foot syndrome (26%). The median time to progression was 11.5 months (347.5 days) with 95% confidence intervals of 6.8–12.9 months (206–389 days). The time to progression ranged from 1.8 to 34 months. The median survival of the patients in this trial was 31.28 months (952 days) with a confidence interval of 20.9–38.0 months (629–1141 days). Intravenous infusion of floxuridine and leucovorin is beneficial as first-line therapy in advanced colorectal cancer, demonstrating a prolonged time to progression and overall survival with acceptable tolerability and manageable toxicity profile. *Anti-Cancer Drugs* 18:955–961 © 2007 Lippincott Williams & Wilkins.

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Introduction

Colorectal cancer is the second leading cause of cancer-related deaths in the US and accounts for 10–15% of all cancers. Approximately 148 000 new cases of colorectal cancer are diagnosed annually. It is estimated that nearly 57 100 deaths from colorectal cancer occurred in 2003 [1]. Fifty percent of colon cancer patients are diagnosed with distant metastases, either at the time of initial presentation or as a result of disease recurrence. Chemotherapy has become standard treatment for most patients with advanced colorectal cancer. The new regimens have improved the response rate (RR), time to progression (TTP) and median survival of patients in advanced disease, with tolerable side effects. The median survival of these patients has improved from approximately 12 months in the mid-1990s to over 20 months in 2004 [2].

For more than 40 years, 5-fluorouracil (5-FU) has remained the agent of choice for the treatment of colorectal cancer and formed the basis of chemotherapy regimens for metastatic disease. Treatment with bolus 5-FU led to a response rate (RR) not exceeding 12% and median survival of approximately 11 months [2–4]. Modulation of 5-FU with leucovorin (LV), which covalently binds to fluorodeoxyuridine monophosphate (FdUMP), has led to an increase in RR to 23% with little influence on survival [5,6]. Over the past decade, there have been several attempts to increase the efficacy of 5-FU by changing the dose, schedule and route of administration of this agent. Delivering 5-FU by continuous intravenous infusion has slightly improved the RR (22 versus 14% $P < 0.002$), but did not significantly change survival (12.1 months versus 11.3 months $P < 0.04$); however, it has reduced the overall toxicity (grade 3–4 neutropenia 31 versus 4%) [4–8].

Following its approval in the US (1996), irinotecan, a topoisomerase I inhibitor, has undergone extensive clinical evaluation in combination with 5-FU/LV [9–11]. A randomized study of first-line treatment for advanced colorectal cancer compared IFL (125 mg/m^2 irinotecan,

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bolus 500 mg/m^2 5-FU, 20 mg/m^2 LV weekly for 4 weeks followed by 2 weeks rest) with 425 mg/m^2 5-FU and 20 mg/m^2 LV daily for 4 weeks. The IFL regimen significantly demonstrated longer progression-free survival (median, 7.0 versus 4.3 months), a higher RR (39 versus 21%, $P < 0.001$) and prolonged median overall survival (OS) (14.8 versus 12.6 months) [9]. Another trial compared irinotecan, using the Douillard regimen, with infusion 5-FU and LV. The results of this trial showed a RR of 49 versus 31% ($P < 0.001$), median TTP 6.7 versus 4.4 months ($P < 0.001$) and median OS 17.4 versus 14.1 months ($P < 0.031$) in favor of the irinotecan group [10]. On the basis of these randomized trials, IFL was registered for use in the US as first-line therapy for advanced colorectal cancer.

With the introduction of oxaliplatin, the combination of the latter and infusional 5-FU (FOLFOX4) led to a superior OS [11]. Currently, FOLFOX4 is considered by many oncologists to be the first-line therapy for the treatment of advanced colorectal cancer, with a median survival of 19.5 months. All outcome measures for patients receiving FOLFOX4 were significantly better than for those receiving the standard IFL regimen. There was a significantly better TTP for FOLFOX4 compared with IFL (8.7 versus 6.9 months; $P = 0.0014$), higher RR (45 versus 31%; $P = 0.002$) and improved OS (19.5 versus 15 months; $P = 0.0001$). Patients treated with irinotecan and oxaliplatin had a significantly lower median TTP (6.5 months) and RR (35%) compared with FOLFOX4 ($P = 0.001$ and $P = 0.03$, respectively); median survival, however, did not differ significantly between the two regimens (19.5 versus 17.4 months, $P = 0.09$) [11–15]. On the basis of these results, the FOLFOX4 regimen was approved for first-line treatment of patients with advanced colorectal cancer in US and Europe.

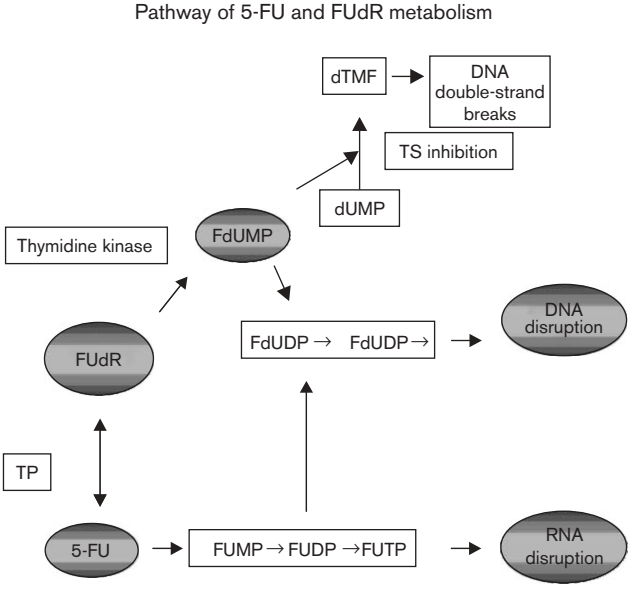
Another first-generation fluoropyrimidine, 5-fluorodeoxyuridine (FUdR), has also shown antineoplastic activity in a wide range of solid neoplasms [16,17]. Our in-vitro studies have shown that FUdR is at least 100-fold more active than 5-FU at equimolar concentrations, when examined in a panel of human cancer cell lines [18,19]. FUdR, the deoxynucleoside metabolite of 5-FU, can be converted in a single step to FdUMP, which binds covalently to thymidylate synthase (TS) and is a powerful inhibitor of TS [20]. Both fluoropyrimidines (5-FU and FUdR) exert part of their antitumor effects via FdUMP inhibition of TS, resulting in the reduced availability of thymidine (from dUMP) inhibiting DNA synthesis, enhancing DNA strand breaks and ultimately leading to apoptosis (Fig. 1). FUdR is transported more rapidly across the plasma membrane as it is more soluble than 5-FU (a nucleoside versus a base) [21]. A variety of cancer cells have demonstrated low concentrations of deoxyribose sugar [16]. This deficiency will be the rate-limiting factor for 5-FU to acquire the respective deoxyribose sugar before activation [16]. FUdR is one step away from its active metabolite FdUMP, which, in the presence of methylene tetrahydrofolate (N^5N^{10}), binds covalently to the target enzyme TS. Thus, by administering FUdR, we have attempted to bypass this rate-limiting step in the anabolism of 5-FU (Fig. 1). Traditionally, the clinical use of FUdR has been 'liver-directed' therapy via hepatic artery infusion. This regional treatment has been effective in treating colonic malignancy localized only in the liver [22–24]. Disease outside the liver was not affected by this treatment and a systemic approach had to be investigated. We realized that FUdR is an effective agent; however, it had to be used systemically. As FUdR has a half-life of 15 min, we infused the patient with this agent for the minimum of 24 h every week, relying on our previous experience with the use of 5-FU, which had been infused over 24 h every week [7]. Initially, we conducted a phase I study of FUdR and determined the maximum tolerated dose to be 150 mg/kg administered as a 24-h weekly infusion [25,26]. In our current phase II study, we incorporated IFLUX in the treatment of previously untreated advanced metastatic colorectal cancer patients.

Materials and methods

Patient eligibility

The eligibility criteria were histological confirmed adenocarcinomas of the colon or rectum. All patients

Fig. 1



TS-Thymidylate synthase, dUMP-Deoxyuridine monophosphate, TP-Thymidine phosphorylase, FdUDP-5-Fluorouridine diphosphate, FU-Fluorouridine, FdUTP-5-fluorodeoxyuridine triphosphate, FdUMP-Fluorodeoxyuridine monophosphate, FUTP-5-Fluorouridine triphosphate, FdTMP-Fluorodeoxythymidine monophosphate, dTMP-Deoxythymidine monophosphate.

had advanced unresectable metastatic disease (stage IV/Duke D stage) with life expectancy of at least 12 weeks. Metastases were defined as at least one bidimensionally measurable lesion > 10 mm diameter. All obstructive lesions of the bowel were bypassed or decompressed. Additional requirements were adequate hematologic status as evidenced by a pretreatment absolute neutrophil count > 2000/mm^3 and a platelet count > 100 000/mm^3, adequate renal function (serum creatinine concentration $\leq$ 2.0 mg/dl), aspartate aminotransferase and alanine aminotransferase two times the institutional normal level in the absence of liver involvement, and with metastatic disease up to five times the institutional normal level. Patients should not have received previous chemotherapy for advanced colorectal cancer. Prior adjuvant chemotherapy was allowed if 1 year had elapsed after discontinuation of treatment. Prior local radiation therapy was allowed in the patient with rectal cancer. Prior surgery and radiation therapy were allowed with a 1-month interval for recovery (Eastern Clinical Oncology Group performance status of 0–2; age > 18 years). Written voluntary informed consent was a requirement for study entry. A double-lumen port-a-cath was surgically placed before the start of therapy. The protocol was approved by the Institutional Review Board at the Sylvester Comprehensive Cancer Center, University of Miami.

Thirty-eight patients with previously untreated metastatic colorectal cancer were enrolled in this nonrandomized trial from 2000 to 2004. Primary disease sites were as follows: colon 66% (25 patients) and rectum 34% (13). All patients had metastatic disease, 42% (16) to the liver, 8% (3) to the lung, 13% (5) to the liver and lung and 37% (14) to other sites. There were 22 men, 16 women, 10% (4) black, 47% (18) hispanics, 42% (16) white and their ages ranged from 28 to 81 years (median 62). The median Karnofsky performance status was 90. Adjuvant chemotherapy had been administered to 55% (21); 45% (17) had not been treated before. In this study, there were 766 chemotherapy sessions in all and there was an average of five cycles of chemotherapy completed per patient (Table 1).

Table 1 Baseline characteristics (n = 38)

Age range	28–81 years
Median	62 years
Men	22 (58%)
Women	16 (42%)
Ethnicity	
Black	4 (10%)
Hispanic	18 (47%)
White	16 (42%)
Site of disease	
Colon	25 (66%)
Rectum	13 (34%)
Distant metastasis	38
Liver	16 (42%)
Lung	3 (8%)
Liver and lung	5 (13%)
Other sites	14 (37%)
Median KPS	90
100	16 (43%)
90	10 (16%)
80	9 (23%)
70	3 (8%)
60	0
50	0
Previously treated (adjuvant)	21 (55%)
Previously untreated	17 (45%)
Total treatment sessions	766
Average treatments per patient	20
Average cycles completed	5

KPS, Karnofsky performance status.

Table 2 Treatment schema

Week	Day	Agents and dosage		
		Irinotecan 110 mg/m^2 i.v. over 90 min	FUdR 120 mg/kg CI over 24 h	Leucovorin 500 mg/m^2 CI over 24 h
1	1	×	×	×
2	8	×	×	×
3	15	×	×	×
4	22	×	×	×
5 and 6	29 and 36	Rest	Rest	Rest

CI, continuous intravenous infusion; FUdR, 5-fluorodeoxyuridine; i.v., intravenously.

Treatment design and schedules

IFLUX chemotherapy regimen consisted of 110 mg/m^2 irinotecan, intravenously over 90 min followed by combined therapy of 120 mg/kg FUdR and 500 mg/m^2 LV continuous intravenous infusion over 24 h. Treatment cycle consisted of 4 weeks of consecutive treatment followed by 2 weeks of rest (Table 2). The calculation of the dosing of the above agents was based on our earlier phase I study.

FUdR was purchased from Hoffman La Roche Pharmaceutical (Nutley, New Jersey, USA) or American Pharmaceutical Partners (Schaumburg, Illinois, USA).

Irinotecan starting dose of 110 mg/m^2 was administered in 250–500 ml of 5% dextrose in water or 0.9% sodium chloride solution intravenously via an infusion pump over 30–90 min. This was followed by FUdR, starting dose 120 mg/kg in combination with LV at 500 mg/m^2 concurrently administered over 24 h. We had shown earlier that administration of fluoropyrimidines and LV through a single port leads to calcium carbonate deposits within the catheter; therefore, we have taken the precaution of administering FUdR and LV through two separate ports (double-lumen port-a-cath) [27]. All patients received a routine antiemetic with a 5-hydroxytryptamine-3 receptor antagonist before infusion. Granulocyte colony-stimulating factor was administered to the patients who demonstrated nadir counts of absolute neutrophil counts below 1000/mm^3. Erythropoietin was initiated at Hgb < 9.9 mg/dl and/or Hct < 29.9%, and was continued until Hgb > 12, and/or Hct > 36, according to institutional guidelines. In patients who experienced grade > 2 hematological or nonhematological toxicity the dose of

chemotherapy was maintained. If the patient had hematologic or nonhematologic toxicity of grade > 3, the dose of CPT-11 was reduced from 110 to 100 mg/m^2, the dose of FUdR was reduced from 120 to 110 mg/kg and LV dose remained the same. Thereafter the patient continued therapy at the reduced doses.

Patients were assessed before each visit using the National Cancer Institute Common Toxicity Criteria version 2 [28]. The major reason for removal from the study was disease progression.

Each patient received an average of five cycles of treatment, the median number of the treatments were 20. A total of 766 therapies were given in this trial. Seventeen (45%) of the patients were chemotherapy naive and 21 (55%) patients had earlier received 5-FU-based adjuvant therapy. Nine (24%) patients with rectal tumor had received local radiation therapy.

Study parameters

Thirty-eight patients were referred to Sylvester Comprehensive Cancer Center, University of Miami, between 2000 and 2004 for assessment and treatment of advanced colorectal cancer. Karnofsky performance status was assessed weekly [29]. Physical examination and blood counts were performed at every visit. Hepatic and renal function tests, carcinoembryonic antigen, and computed tomography (CT) scans of measurable lesions were assessed at baseline and repeated every 8 weeks.

Objective tumor response and survival were assessed according to the World Health Organization criteria [30]. Serial spiral CT scanning was used to assess all measurable disease. Complete response (CR) was defined as disappearance of all known disease determined by two observations not less than 4 weeks apart. Partial response (PR) was defined as a 50% or more decrease in the sum of the longest diameter of target lesions identified at baseline as determined by two observations not less than 4 weeks apart. Stable disease (SD) was defined as no appearance of new lesions and/or no sufficient shrinkage to qualify for partial response. Progressive disease (PD) was defined as an increase by at least 20% in the longest diameter among target lesions, compared with the smallest diameter recorded during treatment, and any appearance of new lesions.

Toxicity was evaluated according to National Cancer Institute guidelines. TTP was measured from the beginning of chemotherapy treatment to the date of the tumor progression confirmed by CT or date of last contact. OS was measured from the beginning of this chemotherapy regimen until the patients' death. After confirmed tumor progression, 18 patients were offered chemotherapy with oxaliplatin, FUdR and LV. Eleven out of 38 (29%) patients underwent resection of tumor in liver or liver and lung.

Statistical consideration

This was a nonrandomized study. Eligible patients were treated with chemotherapy until CR and/or resection of the tumors, or PR and continuation of therapy. Analysis of OS and TTP were performed using the Kaplan–Meier [31,32] method.

Results

Hematological toxicity

Grade 2 and grade 3 hematological toxicities were observed. The most common hematological side effect was leucopenia (34%) treated with neupogen. Anemia was seen in (27%) and treated with weekly injections of erythropoietin. Only one patient required blood transfusion (Table 3).

Nonhematological toxicity

The most frequent grade-3 toxicity was hand-and-foot syndrome (26%), followed by vomiting (24%) and hair loss (18%). Grade-3 diarrhea was seen in 16% of the patients; it was controlled with lomotil and tincture of opium and did not significantly postpone treatment. Grade-3 fatigue was seen in 13% of the patients; however, a majority of patients were able to continue their normal activities in daily life. Antiemetic therapy was used in all patients before therapy (Table 4).

Survival and response rate

Median TTP was 11.5 months (347.5 days) with 95% confidence interval (206, 389) days (Fig. 2). The median survival of the patients who were enrolled in this trial was 31.28 months (952 days) with 95% confidence interval

Table 3 Maximum laboratory-based toxicities – any cycle of treatment

	No. of patients with maximum WHO toxicity grade (% patients)				
Toxicity	0	1	2	3	4
Leukocytes	19 (50%)	6 (16%)	7 (18%)	6 (16%)	0
Hemoglobin	7 (18%)	21 (55%)	4 (11%)	6 (16%)	0
Platelets	22 (58%)	9 (23%)	2 (5%)	5 (13)	0
Alkaline phosphatase	38 (100%)	0	0	0	0
Aspartate transaminase (AST, SGOT)	38 (100%)	0	0	0	0
Alanine transaminase (ALT, SGPT)	38 (100%)	0	0	0	0
Bilirubin	38 (100%)	0	0	0	0

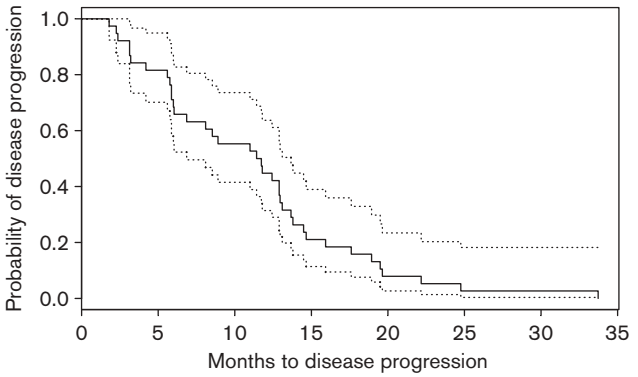
ALT, alanine aminotransferase; AST, aspartate aminotransferase, SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WHO, World Health Organization.

Table 4 Maximum clinical toxicities – any cycle of treatment

	Maximum NCI-CTC toxicity grade (% patients)				
Toxicity	0	1	2	3	4
Constipation	21 (55%)	16 (42%)	0 (3%)	1	0
Diarrhea	10 (26%)	15 (39%)	7 (18%)	6 (16%)	0
Hair loss	20 (53%)	9 (24%)	2 (5%)	7 (18)	0
Nausea	10 (26%)	20 (53%)	2 (13%)	6 (16%)	0
Vomiting	20 (55%)	7 (18%)	3 (8%)	8 (24%)	0
	Hand				
Mucositis	18 (43%)	12 (34%)	2 (5%)	6 (16)	0
Fatigue	7 (18%)	19 (50%)	7 (18%)	5 (13%)	0
Rash	35 (99%)	3 (1%)	0	0	0
Neuropathy	36 (95%)	2 (5%)	0	0	0
Hand/foot syndrome	6 (15%)	12 (31%)	10 (26%)	10 (26%)	0

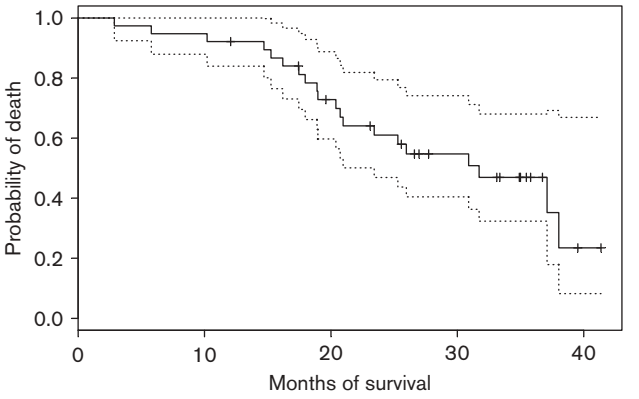
NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Fig. 2



Kaplan–Meier curve time to tumor progression.

Fig. 3



Kaplan–Meier curve for overall survival.

Table 5 Median survival (months) reported in mCRC [reference]

5-FU bolus	11.3 [4]
5-FU infusion	12.1 [4]
5-FU/LV	12.6 [9]
IFL	14.8 [9]
Douillard	16.8 [10]
IROX	17.4 [11]
FOLFOX	19.5 [11]
FOLFIRI/FOLFOX6	21.5 [12]
FOLFOX6/FOLFIRI	20.4 [12]
Current study	31.2

FOLFOX oxaliplatin and infusional fluorouracil (5-FU); IFL, 125 mg/m^2 irinotecan, bolus 500 mg/m^2 5-FU, 20 mg/m^2 leucovorin (LV); IROX, irinotecan and oxaliplatin; mCRC, metastatic colorectal cancer.

(629, 1141) days (Fig. 3). Median TTP was 11.5 months (347.5 days) with 95% confidence interval (206, 389) days (Fig. 2). The TTP ranged between 1.8 and 34 months. All 38 patients were evaluated for response: CR in five (13%), PR in 10 (26%), SD in 17 (45%), and PD in six (16%). An overall response rate of 39% was observed in this study. The patients who failed this first-line regimen were offered second-line therapies that consisted of oxaliplatin, FUdR and LV. Twenty-two (58%) patients were treated with this regiment as a second-line therapy. Two patients were treated with gemzar owing to the limited availability of oxaliplatin during the conduct of this study.

Discussion

Over the past 5 years there have been rapid advances in the treatment of metastatic colon cancer. It was not long ago when the treatment with 5-FU and LV led to a median survival of approximately 1 year (Table 5) [3–5]. Subsequently, with the use of infusional chemotherapy, the median survival was moderately increased to 14 months with reduced toxicities [4–8]. With the development of irinotecan (CPT-11), the use of the combination 5-FU/LV/irinotecan (Saltz regimen) survival increased to 14.4 months [9]. When infusional 5-FU was incorporated with irinotecan, however, median survival increased to over 16.8 months [10]. Oxaliplatin was later used in the treatment of colon cancer. Recently, Goldberg *et al.* [11] reported a median survival of 19.5 months with the use of FOLFOX4.

Currently, targeted therapy against epidermal growth factor receptor and vascular endothelial growth factor (VEGF) are undergoing clinical trials. Bevacizumab (Avastin), anti-VEGF, in combination with IFL leads to a median survival of 20.3 months [33], which is not significantly different from that with FOLFOX4. We are, however, patiently waiting for the result of clinical trials incorporating FOLFOX4 and avastin [34].

We are combining, in this study, the use of FUdR and LV – IFLUX – without the use of targeted therapies. We had reported earlier on the use of FUdR in phase I and phase II studies [25,26]. On the basis of our in-vivo and in-vitro studies, we believe that FUdR has the following

properties: (1) mole for mole, it is significantly more active than 5-FU, (2) it is less toxic than 5-FU and (3) with continuous drug administration, development of tumor resistance occurs less readily with FUdR compared with 5-FU. In this trial, we are reporting on the use of 24-h continuous infusion of FUdR at 120 mg/kg with LV at 500 mg/m^2 being administered concurrently, weekly with irinotecan at 110 mg/m^2 over a 90-min infusion. The FUdR dose used in this trial is near its maximum tolerated dose as a single agent of 150 mg/kg. Furthermore, we have reduced the dose of irinotecan from 125 to 110 mg/m^2 to render the regiment tolerable to our patients. The cycle consists of 4 weeks of treatment followed by 2 weeks of rest. This is the first reported study of the use of three agents including FUdR that has been shown to prolong survival beyond 31.2 months. We speculate that such an improved survival, as reported in this study, was due to (1) the increased resectability rate of the patients, 11 out of 38 became surgically resectable, (2) the use of FUdR in its optimal concentration with irinotecan, which led to a TTP of 11.5 months, and (3) the use of FUdR with oxaliplatin in those patients who failed the initial therapy.

The IFLUX regimen has led to an exceptionally high overall RR of 31.2 months that needs to be confirmed in a randomized phase III study. New targeted inhibitors of the epidermal growth factor receptor (cetuximab) and VEGF (bevacizumab) are now being commonly used in the treatment of colorectal cancer. IFLUX regimen with an acceptable tolerability and toxicity profile is an excellent platform for the addition of biologic agents, which could lead to a better OS of patients with advanced metastatic colon cancer.

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