

ACTIVITY OF IRINOTECAN, CISPLATIN AND DACARBAZINE (CPD) COMBINATION IN PREVIOUSLY TREATED PATIENTS WITH ADVANCED COLORECTAL CARCINOMA

*Hakan Akbulut**, *Fikri Icli*, *Bulent Yalcin*, *Ahmet Demirkazik*, *Handan Onur*,
Abdullah Buyukcelik, *Gungor Utkan*

Department of Medical Oncology, Ibni Sina Hospital, Ankara University Faculty of Medicine, Sıhhiye, Ankara 06100, Turkey

Aim: Irinotecan is an active drug after fluorouracil (FU) failure in patients with colorectal cancer (CRC). Also a modest activity of cisplatin and dacarbazine combination in FU resistant patients have been reported. We aimed to assess the efficacy of irinotecan, cisplatin and dacarbazine combination in previously treated patients with measurable advanced CRC. **Methods:** Treatment schedule was irinotecan 150 mg/m², iv, d1; cisplatin 20 mg/m² and dacarbazine 200 mg/m² iv, d1-d3; every 21 days. 48 patients with a median age of 51 were entered the study. **Results:** Objective response rate was 33.3%. The overall disease stabilization rate was 75.6%. The median survival was 14 months, and the median progression-free survival was 7 months. Main toxicities were grade 2–3 vomiting (39.2%) and grade 3–4 neutropenia (17.4%). **Conclusion:** CPD combination seems to be very active, with acceptable safety profile, in patients with advanced CRC resistant to FUFA.

Key Words: advanced disease, cisplatin, colorectal carcinoma, dacarbazine, irinotecan.

Fluorouracil (FU) has been the standard chemotherapeutic agent for the treatment of advanced colorectal carcinoma, since its introduction into clinical practice. However, the response rates with single agent FU or its modulations with folinic acid or others vary between 15 to 40% [1]. Irinotecan is reported to be effective in patients with colorectal carcinoma (CRC) resistant to FU [2, 3]. Recently, irinotecan and FU and folinic acid (FUFA) combination has been reported to prolong the survival of patients with advanced colorectal carcinoma when compared to FUFA alone [4, 5]. However, there is no known drug to be effective in irinotecan resistant patients. Previously, we reported a favorable response rate with cisplatin + dacarbazine regimen in patients with advanced CRC [6]. In this study, we evaluated the efficacy of irinotecan, cisplatin and dacarbazine combination (CPD) in previously treated patients with advanced CRC.

PATIENTS AND METHODS

Patient selection. Patients with (1) advanced or recurrent CRC; (2) resistant to FUFA (MAYO regimen)/irinotecan following FUFA failure; (3) age 20–70 years; (4) ECOG performance status 2 or less; (5) adequate bone marrow reserve; normal renal functions were eligible for the study. Resistance to FUFA was defined as progressive disease during the treatment. Also, patients failed to respond irinotecan alone following FUFA regimen were included in the study. Resistance to irinote-

can was defined as progression while under treatment or within 3 months following at least 4 cycles of treatment which resulted as stable disease.

Treatment and assessment. The treatment schedule was Irinotecan (Campto®) 150 mg/m², d1, cisplatin 20 mg/m²/d, d1–3 and dacarbazine 200 mg/m²/d, d1–3. After getting informed consent, the treatment was given every 3 weeks until disease progression, any unacceptable toxicity or patient refusal.

Primary end point was response rate. Secondary end points were progression-free survival (PFS) and overall survival (OS). Response to treatment was assessed every 2 cycles according to WHO criteria. All patients had CT evaluation of abdomen and/or thorax every 2 cycles depending on the disease site. Response rates were assessed in patients who received at least 2 cycles of the treatment (response evaluable patients).

Statistical considerations. The optimal two-stage design with a lower activity level P0 of 0.10 and a target activity level P1 of 0.30 was selected for accrual and sample size [7]. It was planned to increase the number of patients to assess the response rate with more precision. Survivals were estimated in all enrolled patients (intention to treat basis) by the method of Kaplan—Meier.

RESULTS

Patients characteristics. Between November 1998 and September 2000, 48 patients (28 treated with only FUFA, 20 with irinotecan after FU failure) were entered the study. Median follow-up time was 15 months. Patient characteristics are shown in Table 1. 45 out of 48 patients were evaluable for response rates. 2 patients refused to take more treatment following the first cycle and 1 patient died of an unknown cause outside the hospital before response evaluation. 2 patients were

Received: April 7, 2004.

*Correspondence: Fax: +90-312-312 1650

E-mail: hakbulut@dialup.ankara.edu.tr

Abbreviations used: FU — fluorouracil; CRC — colorectal carcinoma; FUFA — FU and folinic acid; PFS — progression-free survival; OS — overall survival; CPD — irinotecan, cisplatin and dacarbazine; EGFR — epidermal growth factor receptor;

Table 1. Patient characteristics

Table 1. Patient characteristics	
Number, enrolled	48
Lost to follow-up	2 (4.2%)
Number, Response Evaluable	45
Median age (range)	51 (31–70)
Gender	
Female	18
Male	27
PS (ECOG) (%)	
0	11 (24.6)
1	17 (37.7)
2	17 (37.7)
Site of Primary tumor	
Rectum	15 (33.3%)
Colon	30 (66.7%)
Metastatic sites	
Liver	30
Local/lymph node	16
Lung	11
Periton	8
Bone	5
Other	3
No. of metastatic sites	
1	21
2	20
>=3	4
Previous chemotherapy/adj. radiotherapy	
FUFA	45
irinotecan	20
Radiotherapy	6
Median time from the diagnosis of metastatic disease to the enrollment (months)	5 ± 1 (95% CI: 3–8)

lost to follow-up. 46 patients were included in the survival analysis.

All of the patients were resistant to FUFA and 20 of them were also resistant to irinotecan (300–350 mg/m², q3w) alone. Disease progressed in 13 of 20 patients under irinotecan treatment. In the other 7 patients irinotecan was discontinued following 4 cycles, because there was no response. However all 7 had progressive disease in less than 3 months following the termination of irinotecan.

Response. There were 15 objective responses (2 complete responses and 13 partial responses) with an overall response rate of 33.3% (Table 2). Most of the responses (13/15) were observed in patients with liver and/or lung metastases. 2 partial responder patients, initially unresectable (one with multiple liver metastases resistant to FUFA and the second one with local and lymph node recurrence resistant to both FUFA and irinotecan), had curative resection after CPD treatment (after 4 cycles and 8 cycles, respectively), and are tumor-free at the seventh and fifth months of resection, respectively. Disease stabilization rate was 75.6%.

Interestingly, there were 6 partial responses in 20 patients who received irinotecan previously (30.0%) (see Table 2). 3 of these 6 patients had progressive disease while receiving irinotecan. Three patients failed to respond

Table 2. Treatment outcomes — response rates

	Evaluable patients (n = 45) (%)	Subset of patients re- ceived Irinotecan be- fore (n = 20) (%)
Complete response	2 (4.4)	—
Partial response	13 (28.9)	6 (30.0)
Overall response	15 (33.3)	6 (30.0)
Stable disease	19 (42.2)	8 (40.0)
Disease stabilization rate	34 (75.6)	14 (70.0)
Progression	11 (24.4)	6 (30.0)

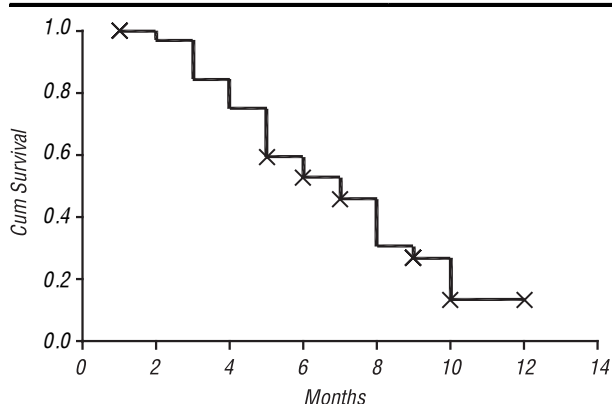
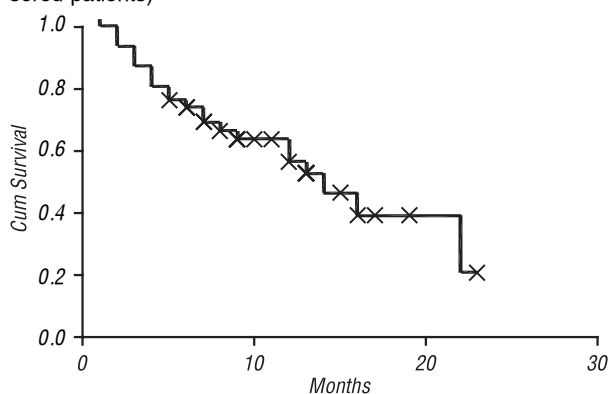
to irinotecan after 4 cycles and disease progression was observed within 2 months following the treatment.

Significant improvement in performance status (ECOG) was seen in 47.3% of the symptomatic patients.

Survival. Median progression-free survival time was 7 months. Median response duration time was 6 months. While the median overall survival time from the diagnosis of the metastatic disease was 22 months, it was 14 months from the time of enrollment to the study (Table 3). The 54% of the patients were alive 1 year after study enrollment. The PFS and OS curves are shown in Fig. 1 and 2.

Table 3. Treatment outcomes — time-related variables

Variables	Median time, months
Response duration	6 ± 1 (95% CI 3–8)
Progression-free survival	7 ± 1 (95% CI 5–9)
Overall survival from enrollment	14 ± 3 (95% CI 9–19)
Overall survival from the diagnosis of metastatic disease	22 ± 3 (95% CI 17–27)

**Fig. 1.** Progression-free survival curve of the patients (x — censored patients)**Fig. 2.** Overall survival curve of the patients according to intent-to-treat principle (x — alive patients)**Table 4.** Toxicity profile

Toxicities (WHO grade)	Number of the patients (%)
Acute cholinergic syndrome	8.7
Neutropenia	
Grade 1	17.4
Grade 2	15.2
Grade 3	13.0
Grade 4	4.4
Delayed diarrhea	
Grade 1	19.6
Grade 2	17.4
Grade 3	7.7
Grade 4	4.4
Nausea/vomiting	
Grade 1	17.4
Grade 2	34.8
Grade 3	4.4

Toxicity. The toxicities were acceptable (Table 4). Febrile neutropenia was seen in only one patient (2.2%). Two patients were hospitalized for parenteral support because of grade IV delayed diarrhea.

DISCUSSION

Since its synthesis in 1957, FU has been the primary chemotherapeutic agent in advanced colorectal carcinoma. No other single agent, more than 80 drugs studied till now, found to be superior than FU in colorectal carcinoma [1, 8]. Protracted infusions, biochemical modulations and higher doses of this drug have been reported to produce response rates up to 40% [1]. However, the median survival of the patients with advanced CRC yielded by the best FU regimens was 10–12 months [9].

Recently, irinotecan and oxaliplatin were found to yield response rates of not more than 15% in FU resistant patients in phase II trials [10–12]. In 1998, a survival advantage of irinotecan alone with response rates around 10% over either supportive care or continuous FU infusion in FU resistant advanced CRC patients have been reported [2, 3]. In the current study, the objective response rate was 33.3% (4.4% complete response and 28.9% partial response). This impressive response rate with a median duration of 6 months are encouraging. Also a very high disease stabilization rate of 75.6% with a median period of 7 months was observed. Though quality of life assessment was not done in this non-randomized trial, a significant improvement in performance status of the patients was achieved in 47.3% of the symptomatic patients. The median overall survival of 14 months is also comparable to those reported before [2, 3, 10].

Recently, Douillard JY et al with the combination of a weekly and biweekly schedules of irinotecan and two different FU regimens including high dose folinic acid, and Saltz LB et al, with the combination of a weekly schedule of irinotecan and FU plus low dose FA have reported increased response rates and prolonged survivals when compared to FUFA regimens used in the irinotecan arms [4, 5]. In the trial of Irinotecan Study Group, a third arm of weekly irinotecan alone yielded similar results to the FUFA arm [5]. Currently, irinotecan and FUFA combination is widely accepted as the new standard treatment of advanced CRC. However, new drugs or combinations to be effective in patients who are refractory or resistant to this new standard are needed. There is no known effective regimens of choice for this purpose yet. In combination with FA modulated FU, oxaliplatin has been reported to have a small activity following irinotecan in patients with CRC [13]. However, very recently Chau I et al [14] has reported a 27.3% objective response rate in a subset of 22 irinotecan resistant out of 38 previously treated patients group with oxaliplatin plus protracted FU infusion. Patel J et al [15] also has reported 21% response rate in advanced CRC patients previously treated with irinotecan. In their recent pilot study in a group of 32 heavily pretreated (including irinotecan) advanced CRC patients, Levi F et al [16] reported only 2 responses with

chronomodulated schedule of irinotecan, fluorouracil, leucovorin and oxaliplatin combination. Very recently, Saltz L et al [17] have reported an impressive response rate of 17% in patients with epidermal growth factor receptor (EGFR) positive, irinotecan refractory CRC with cetuximab (IMC-C225), a chimeric monoclonal antibody selectively binding EGFR, plus irinotecan.

Previously, we reported a favorable response rate of 19% in FU resistant patients with cisplatin and dacarbazine combination [6]. In the current study, 6 out of 20 patients previously received FUFA and irinotecan responded to CPD regimen (see Table 2). To our knowledge this is the highest response rate of a regimen after irinotecan failure in advanced CRC patients. This highly impressive response rate of CPD indicates a synergistic activity of irinotecan with cisplatin and dacarbazine.

Resection of CRC metastases, mainly liver, have been reported to produce about 30% survival at 5–years with a cure chance of some patients [18, 19]. Regarding this possibility, one of the goals of therapy to improve survival in advanced CRC patients, initially unresectable, should be an acceptable response to make resection possible. In this study, the metastatic tumors of 2 patients, who were unresectable before, were resected following CPD regimen. These patients are still tumor-free at the seventh and fifth months of resection, respectively.

The toxicity profile of CPD regimen was manageable. The most frequent adverse event was grade 2–3 nausea/vomiting (Table 4). However, grade 3–4 delayed diarrhea was seen reasonably lower than those trials including irinotecan [2–5, 10, 11]. The hematologic toxicity was also in acceptable limits.

In conclusion, CPD combination with this schedule of administration is an effective regimen in patients with advanced CRC resistant to fluorouracil, and also seems to be effective after irinotecan failure.

REFERENCES

1. Cohen AM, Minsky BD, Schilsky RL. In: Cancer of the colon. De Vita VT, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*, Fifth ed. Philadelphia: J.B.Lippincott Co., 1997; 1144–96.
2. Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C, Herait P. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998; **352**: 1413–8.
3. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques C. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998; **352**: 1407–12.
4. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first line treatment for metastatic colorectal cancer: a multicenter randomised trial. *Lancet* 2000; **355**: 1041–7.
5. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK,

Pirota N, Elfring GL, Miller LL. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer: Irinotecan Study Group. *N Engl J Med* 2000; **343**: 905–4.

6. **Icli F, Arican A, Cay F, Akbulut H, Dincol D, Karaoguz H, Demirkazik A.** Phase II study of cisplatin and dacarbazine for metastatic colorectal carcinoma resistant to 5-fluorouracil. *Oncology* 1999; **56**: 297–300.

7. **Simon R.** Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10**: 1–10.

8. **Punt CJ.** New drugs in the treatment of colorectal carcinoma. *Cancer* 1998; **83**: 679–89.

9. The Advanced Colorectal Cancer Meta-Analysis Project: modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; **10**: 896–903.

10. **Rougier P, Bugat R, Douillard JY, Culine S, Suc E, Brunet P, Becouarn Y, Ychou M, Marty M, Extra JM, Bonnetterre J, Adenis A, Seitz JF, Ganem G, Namer M, Conroy T, Negrier S, Merrouche Y, Burki F, Mousseau M, Herait P, Mahjoubi M.** Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naïve patients and patients pretreated with fluorouracil-based chemotherapy. *J Clin Oncol* 1997; **15**: 251–60.

11. **Bleiberg H.** CPT-11 in gastrointestinal cancer. *Eur J Cancer* 1999; **35**: 371–9.

12. **Machover D, Diaz-Rubio E, de Gramont A, Schilf A, Gastiaburu JJ, Brienza S, Itzhaki M, Metzger G, N'Daw D, Vignoud J, Abad A, Francois E, Gamelin E, Marty M, Sastre J, Seitz JF, Ychou M.** Two consecutive phase II studies of oxaliplatin (L-OHP) for treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines. *Ann Oncol* 1996; **7**: 95–8.

13. **Comella P, De Vita F, De Lucia L, Casaretti R, Avallone A, Orditura M, Rivellini F, Palmeri S, Cata-**

lano G, Comella G. Oxaliplatin and raltitrexed combined with leucovorin-modulated 5-fluorouracil i.v. bolus every two weeks: a dose finding study in advanced previously treated colorectal carcinoma. *Ann Oncol* 2000; **11**: 461–8.

14. **Chau I, Webb A, Norman A, Massey A, Hill M, Cunningham D.** A phase II study of protracted venous infusion (PVI) 5-fluorouracil and oxaliplatin in patients with advanced or relapsed, 5-FU pretreated colorectal cancer. *Proc ASCO* 2001; **20**: 140a (Abstract No:557).

15. **Patel J, Kemeny N, Gonen M, DiLauro C, Stockman J.** A study of continuous infusion (CI) of fluorouracil (FU) and oxaliplatin (OXA) for previously treated colorectal cancer patients. *Proc ASCO* 2001; **20**: 143a (Abstract No:568).

16. **Levi F, Zidani R, Coudert B, Giacchetti S, Brezault-Bonnet C, Manoux D, Dessard-Diana B, Maoudj E, Franco D, Adam R.** Chronomodulated irinotecan (I)-fluorouracil (F)- leucovorin (L) – oxaliplatin (O) (Chrono IFLO) as salvage therapy in patients with heavily pretreated metastatic colorectal cancer (MCC). *Proc ASCO* 2001; **20**: 139a (Abstract No:552).

17. **Saltz L, Rubin M, Hochster H, Tchekmeydian NS, Waksal H, Needle M, LoBuglio A.** Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11 refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR). *Proc ASCO* 2001; **20**: 3a (Abstract No:7).

18. **Scheele J, Stang R, Altendorf-Hoffmann A, Paul M.** Resection of colorectal liver metastases. *World J Surg* 1995; **19**: 59–71.

19. **Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF.** Liver resection for colorectal metastases. *J Clin Oncol* 1997; **15**: 938–46.

ПРИМЕНЕНИЕ КОМБИНАЦИИ ИРИНОТЕКАНА, ЦИСПЛАТИНА И ДАКАРБАЗИНА ДЛЯ ЛЕЧЕНИЯ БОЛЬНЫХ ПРОГРЕССИРУЮЩИМ КОЛОРЕКТАЛЬНЫМ РАКОМ, РАНЕЕ ПОЛУЧАВШИМ ЛЕЧЕНИЕ

Цель: для лечения больных колоректальным раком (CRC), не поддающегося терапии флуороурацилом, может быть успешно применен иринотекан или комбинация цисплатина и дакарбазина (CDDP, DTIC) с FU. Авторы оценивали эффективность комбинации иринотекана, CDDP и DTIC (CPD) в лечении больных прогрессирующим колоректальным раком. **Методы:** схема терапии включала применение иринотекана по 150 мг/м², в/в, д1; CDDP по 20 мг/м² и DTIC по 200 мг/м² в/в, д1–д3; в течение каждого 21 дня. Обследованы 48 больных (средний возраст которых составил 51 год). **Результаты:** объективный уровень ответа составил 33,3%; общий уровень стабилизации заболевания – 75,6%; средняя выживаемость – 14 мес, средняя продолжительность жизни без прогрессирования болезни – 7 мес. Основными токсическими проявлениями были рвота 2–3 степени (39,2%) и нейтропения 3–4 степени (17,4%). **Выводы:** применение комбинации CPD в терапии больных CRC с устойчивостью к FURA весьма эффективно и относительно безопасно.

Ключевые слова: прогрессирующее заболевание, цисплатин, колоректальная карцинома, дакарбазин, иринотекан.