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ORIGINAL ARTICLE

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# Phase I study of CPT-11 and bolus 5-FU/*l*-leucovorin in patients with metastatic colorectal cancer

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**Abstract**
***Background.*** Irinotecan (CPT-11) and bolus 5-fluorouracil (5-FU)/leucovorin (LV) administered weekly for 4 weeks every 42 days (Saltz regimen) is active but substantially toxic in patients with metastatic colorectal cancer (CRC). The efficacy and toxicity of this regimen, however, have not been determined in Japanese patients with metastatic CRC.
***Methods.*** We investigated the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and recommended phase II dose (RD) for CPT-11 given i.v. (90-min infusion) and bolus 5-FU plus biologically active *l*-LV administered weekly for 3 weeks every 28 days (modified Saltz regimen) in Japanese patients with metastatic CRC. Eighteen patients with measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, and adequate organ functions were enrolled.
***Results.*** At dose level 2 (CPT-11, 100 mg/m$^2$; 5-FU, 400 mg/m$^2$; and *l*-LV, 25 mg/body), 1 of 6 patients had DLT (febrile neutropenia). At dose level 3 (CPT-11, 100 mg/m$^2$; 5-FU, 500 mg/m$^2$; and *l*-LV, 25 mg/body), 2 of 6 patients had DLT (febrile neutropenia and grade 4 neutropenia lasting more than 4 days). To determine whether level 3 was the MTD level, an additional 3 patients were treated at this level, but no DLT was observed. Consequently, 2 of 9 patients had DLT at level 3, this level thus being considered as the RD. At this level, grade 3–4 neutropenia was common but manageable. Nonhematological toxicities were mild. Seven partial responses were observed in the 18 enrolled patients (response rate [RR], 39%), and 8 patients (44%) experienced stable disease.
***Conclusion.*** This CPT-11/5-FU/*l*-LV regimen administered weekly for 3 weeks every 28 days has substantial antitumor activity, with manageable toxicities. A multicenter phase II study is currently underway.

**Key words** 5-Fluorouracil · Irinotecan · *l*-Leucovorin · Phase I · Colorectal cancer

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## Introduction

The incidence of colorectal cancer (CRC) is increasing worldwide. Currently, approximately 30% of CRC patients present with advanced disease, and the standard treatment for those patients has been 5-fluorouracil (5-FU)-based chemotherapy, which has been demonstrated to prolong survival and to improve quality of life.[1–3] 5-FU is commonly administered with leucovorin (LV) to augment the inhibition of thymidylate synthetase by 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP), an active metabolite of 5-FU.[4] This combination has been shown to significantly improve response rates and prolong survival with high- and low-dose LV schedules.[5,6] However, the low-dose LV schedule appears to have a superior therapeutic index, compared with the high-dose schedule, and shows similar therapeutic effectiveness, lower financial cost, and less need for hospitalization.[7]

Irinotecan (CPT-11) is a potent inhibitor of topoisomerase I,[8,9] and has demonstrated antitumor activity against metastatic CRC when used alone as first-line[10–12] or second-line treatment after the failure of fluorouracil.[13–15] CPT-11 and 5-FU have different mechanisms of action and appear to exhibit synergistic interaction.[16,17] Thus, two large randomized trials were conducted in the United States and Europe, demonstrating that the addition of CPT-11 to 5-FU and LV significantly improved response rate, time to pro-

**Table 1.** Dose escalation scheme and response

| Dose level | No. of patients | Irinotecan ($mg/m^2$) | *l*-LV (mg/body) | 5-FU ($mg/m^2$) | Assessable patients | Partial response | Stable disease |
|---|---|---|---|---|---|---|---|
| 1 | 3 | 80 | 25 | 400 | 3 | 1 | 1 |
| 2 | 6 | 100 | 25 | 400 | 6 | 2 | 2 |
| 3 | 9 | 100 | 25 | 500 | 9 | 4 | 5 |
| 4 | 0 | 120 | 25 | 500 | – | – | – |

LV, leucovorin; 5-FU, 5-fluorouracil

gression, and overall survival in patients with metastatic CRC, when compared to 5-FU plus LV.[18,19] The combination of CPT-11 and bolus 5-FU/LV administered for 4 weeks every 42 days (Saltz regimen) as an initial treatment of metastatic disease is being increasingly used, mainly in the United States. However, a study has shown that this combination was associated with an excessive early death rate.[20] That study indicated that high rates of grade 3/4 neutropenia and diarrhea were the principal factors responsible. This finding prompted us to study a modification of the original Saltz regimen that would ameliorate the toxic effects, while preserving the activity. More importantly, the efficacy and toxicity of this regimen has not yet been determined in Japanese patients with metastatic CRC.

The primary objective of the present study was to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and the recommended phase II dose (RD) for the modified Saltz regimen (CPT-11 given i.v. over a 90-min period, with bolus 5-FU plus biologically active *l*-LV, administered weekly for 3 weeks every 28 days) in patients with metastatic CRC.

## Patients and methods

### Patient selection

The main eligibility criteria included a histologically confirmed diagnosis of CRC with metastatic disease; age, 20 to less than 75 years; Eastern Cooperative Oncology Group (ECOG) performance status, 2 or less; measurable disease; leukocyte count, $3500/mm^3$ or more; neutrophil count, $1500/mm^3$ or more; platelet count, $100\,000/mm^3$ or more; serum creatinine 1.5 mg/dl or less; serum bilirubin 2.0 mg/dl or less and aspartate aminotransferase (AST) 100 IU/l or less, alanine aminotransferase (ALT), 100 IU/l or less; and a life expectancy of 3 months or more. Previous use of fluoropyrimidine derivatives was allowed. This study was approved by the local ethics committee, and patients were informed of the investigational nature of the study and provided their written informed consent before registration in the study.

Patients with the following criteria were not eligible: central nervous system metastasis, unresolved bowel obstruction or diarrhea, and known contraindications to fluorouracil (angina pectoris, myocardial infarction in the past 6 months).

### Study design and treatment

The study was designed as a phase I dose-finding study to determine the maximum tolerated dose (MTD) and recommended dose of CTP-11 and 5-FU/LV. Treatment consisted of CPT-11 in 500 ml of saline, given i.v. over a 90-min period, followed by bolus *l*-LV and 5-FU. The MTD was defined as the dose level associated with the same DLT in at least two out of three, or two out of six patients. DLT was defined as the occurrence of one or more of the following National Cancer Institute (NCI) common toxicity criteria (CTC): grade 3 or greater nonhematologic toxicity, except for nausea and vomiting; grade 4 neutropenia lasting for more than 4 days; grade 3 neutropenic fever; or grade 4 thrombocytopenia.

### Drug administration and dose escalation

CPT-11 and 5-FU/*l*-LV were administered on days 1, 8, and 15, and cycles were repeated every 28 days. The starting dose of CPT-11 was $80\,mg/m^2$ plus bolus 5-FU $400\,mg/m^2$ and a fixed dose of *l*-LV 25 mg/body. Dose escalation then proceeded as listed in Table 1; the number of patients treated at each dose level is shown. No intrapatient dose escalation was permitted on the study. The number of patients per dose level was based on any DLT experienced during cycles 1 and 2. If a DLT was observed in one of the first three patients treated at a particular dose level, three further patients were recruited. If the same DLT occurred in two of the six patients, this dose was defined as the MTD, or three additional patients were recruited at this dose level to confirm the MTD. If at least one additional patient suffered from the same DLT (more than three out of nine patients), this dose level was finally regarded as the MTD. If not, this dose level was defined as the RD for phase II studies.

Treatment was continued until evidence of progression, unacceptable toxicity, or patient refusal. Treatment was delayed if, on the planned day of treatment, there was leukopenia (leukocytes less than $3000/mm^2$), platelets less than $100\,000/mm^3$, infectious fever, persistent diarrhea, or nonhematological toxicities greater than grade 3, except for nausea and vomiting. Treatment was discontinued if, on day 8, treatment had been delayed for the above reasons. When treatment was delayed on day 15, the second cycle was restarted on day 22, with CTP-11 and 5-FU reduced by 20%. When a patient experienced DLT on the first cycle, both CPT-11 and 5-FU were reduced by 20% on the second

cycle. In the event of life-threatening toxicities, treatment was definitively interrupted or continued at doses reduced by 50%. To assess the dose intensity of CPT-11 and 5-FU, the relative intensities of these drugs were individually calculated, as the actually delivered doses divided by the intended doses in a given period of time.

To prevent nausea and vomiting, 5-hydroxytryptamine-3 antagonists and/or methylprednisolone 125 mg were administered i.v. before chemotherapy. Loperamide 2 mg was given in the event of delayed diarrhea. Granulocyte (G)-colony-stimulating factor (CSF) was used when neutrophils were reduced to 500/mm$^2$ or there was febrile neutropenia (neutrophils less than 1000/mm$^2$).

### Assessability, toxicity, and response criteria

Pretreatment evaluation included history and physical examination, performance status assessment, complete blood count with differential and platelet counts, complete blood profile, carcinoembryonic antigen, carbohydrate antigen (CA)19-9, urinalysis, ECG, chest radiograph, or computed tomography (CT) scan, abdominal CT scan and/or ultrasonography, and any other appropriate diagnostic procedure to evaluate metastatic sites. During treatment, a physical examination was performed every week, a complete blood cell count twice a week, and blood profile and urinalysis every week. Sites of metastatic disease were re-evaluated every 8 weeks. Chest radiography and/or abdominal ultrasonography or CT scan was repeated at least every 3 months, if there was no evidence of lung or abdominal disease. Toxicities were monitored weekly and were scored according to standard NCI-CTC. Responses were evaluated every 8 weeks according to World Health Organization criteria.

## Results

### Patients' characteristics

Eighteen patients were enrolled in this study. The individual characteristics of the 18 patients treated are summarized in Table 2. There were 9 men and 9 women. The median age was 59 years, with a range of 30 to 73 years. ECOG performance status was 0 to 2 in the 18 patients. Ten patients had received prior chemotherapy of 5-FU/LV (Mayo regimen). Fifty percent of the patients (9/18) had liver metastases, 61% (11/18) of the patients had lung metastases, and 5% (1/18) of the patients had peritoneal dissemination.

**Table 2.** Patient characteristics

| | |
|---|---|
| Total | 18 |
| Male/Female | 9/9 |
| Age (years) | |
| Median | 59.1 |
| Range | 30–73 |
| Performance status | |
| 0 | 8 |
| 1 | 7 |
| 2 | 3 |
| Primary tumor | |
| Colon | 12 |
| Rectum | 6 |
| Previous treatment | 10 |
| Metastatic site | |
| Liver | 9 |
| Lung | 11 |
| Abdomen | 3 |
| Lymph node | 5 |

### Dose escalation

The first three patients received CPT-11 at 80 mg/m$^2$ and 5-FU at 400 mg/m$^2$ and, because after two cycles no DLTs had occurred, the subsequent group of three patients received CPT-11 at 100 mg/m$^2$ and 5-FU at 400 mg/m$^2$ (dose level 2). At this dose level, febrile neutropenia was observed in one patient. Therefore, an additional three patients were recruited at this dose level. However, no DLTs were observed in the second three patients, and dose escalation proceeded to level 3. At dose level 3, six patients were treated, because one patient in the first three patients and one patient in the second three patients had febrile neutropenia and grade 4 neutropenia lasting for 6 days, respectively. Because the DLT (neutropenia) was observed in two of the six patients, dose escalation was discontinued and that dose was defined as the MTD. To confirm whether level 3 was the MTD level, an additional three patients were treated at this dose level, but no DLT was observed. As a result, two of nine patients had DLT at level 3, and this level was considered as the RD. Thus, the recommended phase II dose is CPT-11 100 mg/m$^2$ and 5-FU 500 mg/m$^2$.

### Toxicity

All patients were assessable for toxicities. There was no treatment-related death in the entire number of cycles in the study. A summary of hematological toxicities is listed in Table 3. Neutropenia was the most common toxicity observed in the study. At the second dose level, four of the six patients experienced grade 3 or greater neutropenia, with one patient having febrile neutropenia. Nine patients were treated on dose level 3. Four experienced grade 3 leukopenia and six, grade 3 or greater neutropenia. Among them, two had febrile neutropenia and grade 4 neutropenia lasting for 6 days. Overall, seven patients (39%) and 10 of 92 cycles (11%) required dose reductions of CPT-11 and 5-FU by 20%. Nine of 92 cycles (10%) were delayed for more than 1 week because of neutropenia. G-CSF was used in 12 of 92 cycles (13%) because of grade 4 neutropenia, whether or not it was associated with fever, or because persistent neutropenia on the day of recycle did not permit maintaining the planned weekly schedule. As a result, the relative dose intensities, calculated as the actual dose delivered divided by the intended dose, were 87% and 84% for 5-FU and CTP-11, respectively, at dose level 3.

**Table 3.** Summary of the hematological toxicities experienced

| Dose level | No. of patients | NCI-CTC grade | Number of patients | | | |
|---|---|---|---|---|---|---|
| | | | WBC | Neutrophils | Platelets | Anemia |
| 1 | 3 | 1 | 0 | 0 | 1 | 0 |
| | | 2 | 0 | 0 | 1 | 1 |
| | | 3 | 2 | 2 | 0 | 0 |
| | | 4 | 0 | 0 | 0 | 0 |
| 2 | 6 | 1 | 0 | 0 | 0 | 4 |
| | | 2 | 1 | 1 | 1 | 2 |
| | | 3 | 4 | 1 | 0 | 0 |
| | | 4 | 0 | 3 (1) | 0 | 0 |
| 3 | 9 | 1 | 4 | 1 | 6 | 5 |
| | | 2 | 0 | 1 | 0 | 2 |
| | | 3 | 4 | 3 | 0 | 0 |
| | | 4 | 0 | 3 (2) | 0 | 0 |

Data are expressed as numbers of patients with the listed grade of toxicity as their maximum
Numbers in parentheses indicate numbers of patients with dose-limiting toxicity (DLT; febrile neutropenia; grade 4 neutropenia lasting for more than 4 days)
NCI-CTC, National Cancer Institute common toxicity criteria

**Table 4.** Summary of the nonhematological toxicities

| Dose level | No. of patients | NCI-CTC grade | Number of patients | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Nausea | Vomiting | Diarrhea | Stomatitis | Alopecia | Asthenia |
| 1 | 3 | 1 | 2 | 0 | 1 | 0 | 0 | 1 |
| | | 2 | 0 | 0 | 0 | 0 | 1 | 1 |
| | | 3 | 0 | 0 | 0 | 0 | – | 0 |
| 2 | 6 | 1 | 1 | 0 | 1 | 0 | 2 | 3 |
| | | 2 | 1 | 1 | 0 | 0 | 1 | 0 |
| | | 3 | 0 | 0 | 0 | 0 | – | 0 |
| 3 | 9 | 1 | 5 | 0 | 4 | 1 | 5 | 3 |
| | | 2 | 0 | 0 | 1 | 1 | 2 | 1 |
| | | 3 | 0 | 0 | 0 | 0 | – | 0 |

Data are expressed as numbers of patients with the listed grade of toxicity as their maximum

Effects on platelets were mild. Platelet decreases below $75 \times 10^9$ cells/l (grade 2 or greater) occurred in only 3 out of 92 cycles, or 2 out of 18 patients, but no grade 3 or 4 thrombocytopenia occurred. The effects on RBCs were, likewise, mild. Anemia below 8.0 g/dl (grade 3 or greater) did not occur.

Nonhematological toxicity was not a major problem in this study. The incidences of major nonhematological toxicities, such as nausea, vomiting, diarrhea, stomatitis, alopecia, and asthenia are listed in Table 4. Slight vomiting (grade 2) was observed in only one patient. On each dose level, there were no toxicities greater than grade 2. Even at the third dose level, grade 2 or greater nausea was not observed in the nine patients. Among these nine patients, one patient experienced grade 2 diarrhea; one, grade 2 stomatitis; and one, grade 2 asthenia, and two patients had grade 2 alopecia.

### Response

Response to therapy was a secondary outcome and was measured in all patients. All patients were assessable for response. Of the 18 patients, 7 experienced a partial response (PR), and 8 had stable disease (Table 1). A response rate of 38.9% was observed. Interestingly, at dose level 3, PRs were observed in 4 of 9 patients (response rate, 44%). In the 10 previously treated patients, three PRs were obtained, while four PRs were observed in the 8 previously untreated patients. Therefore, the previously untreated patients appeared to respond at a much higher rate than the previously treated patients.

## Discussion

The Saltz regimen, which includes CPT-11 125 mg/m$^2$ and bolus 5-FU 500 mg/m$^2$ plus LV 20 mg/m$^2$, administered weekly for 4 weeks every 6 weeks, has demonstrated superiority over 5-FU/LV in terms of response rate, time to progression, and overall survival.[18] However, an excessive death rate (4.8%) within 60 days of starting therapy has been reported.[20] According to the studies of the North Central Cancer Treatment Group (N9741) and Cancer and

Leukemia Group B (C89803), patients treated with CPT-11 plus bolus 5-FU/LV had a threefold higher rate of treatment-induced or treatment-exacerbated death than patients treated either with oxaliplatin plus 5-FU/LV or oxaliplatin plus CPT-11.[20,21] In the N9741 study, 12 of the 14 deaths had several characteristics in common, such as dehydration resulting from vomiting and diarrhea, neutropenia, and sepsis. Thus, high rates of grade 3/4 neutropenia and concomitant severe diarrhea were considered to be the principal factors responsible for the mortality. Therefore, this randomized study was temporarily closed, and subsequently, the initial doses of CPT-11 and 5-FU were reduced, from 125 mg/m$^2$ to 100 mg/m$^2$, and from 500 mg/m$^2$ to 400 mg/m$^2$, respectively, when patients were newly enrolled.

In order to ameliorate such toxic effects of the Saltz regimen, we modified the original schedule from weekly administration for 4 consecutive weeks to 3 consecutive weeks. The original Saltz regimen was associated with grade 3/4 vomiting (9.7%) and diarrhea (22.7%), as well as grade 3/4 neutropenia (53.8%) and neutropenic fever (7.1%).[18] By contrast, grade 3/4 vomiting and diarrhea were not observed with our modified Saltz regimen, at the recommended dose (CPT-11, 100 mg/m$^2$; 5-FU, 500 mg/m$^2$; *l*-LV, 25 mg/body), although grade 3/4 neutropenia (66%) and febrile neutropenia (11%) occurred at frequencies similar to those with the original Salz regimen. However, the toxicities were largely manageable. Consequently, we could continue the treatment schedule as planned in most patients, with a relative dose intensity of 87% with 5-FU and 84% with CPT-11. This is in contrast with the Saltz regimen, where the full doses of CPT-11 and 5-FU/LV could not be administered on the schedule in most patients, and the median relative dose intensities of 5-FU and CPT-11 were 71% and 72%, respectively.[18] There seemed to be no difference in toxicities between previously untreated and previously treated patients with our regimen.

At our recommended doses (level 3), the scheduled dose intensities were 10% less with CPT-11, but 12.5% more with 5-FU when compared with the respective dose intensities of the original Saltz regimen. The lower dose intensity of CPT-11 may account for the absence of grade 3/4 vomiting or diarrhea in our modified regimen. Although the frequency of neutropenia and febrile neutropenia did not differ between the Saltz regimen and our regimen, the absence of concurrent severe diarrhea and vomiting may contribute to the safety of our regimen, with manageable toxicities.

The original Saltz regimen was empirically selected to combine four weekly infusions of CPT-11 with simultaneously administered 5-FU plus *d*,*l*-LV. The *d*,*l*-LV is a racemic mixture of the biologically active *l*-isomer and the biologically inactive *d*-isomer.[22] Administration of 5-FU in the Saltz regimen is based on the Roswell Park schedule of 5-FU/*d*,*l*-LV. Major differences in the Saltz regimen from the Roswell Park 5-FU/*d*,*l*-LV regimen were a reduction of the dose of *d*,*l*-LV to 20 mg/m$^2$ from 500 mg/m$^2$ and the preference of four weekly treatments over 6 consecutive weeks. Regarding the *l*-LV dose in the present regimen, we selected a fixed dose of 25 mg/body rather than 20 mg/m$^2$, not only because the optimal concentration of LV to effectively modulate 5-FU varies substantially depending on the experimental system but also because *l*-LV has been shown to be clinically equivalent to either the same or a double dose of *d*,*l*-LV in its antitumor activity against colon cancer.[23,24]

A recent randomized phase II study revealed that oxaliplatin, a 1,2-diaminocyclohexane platinum compound, in combination with CPT-11, has equivalent clinical activity to other 5-FU-based combinations, with manageable toxicity.[25] Moreover, oxaliplatin, in combination with 5-FU/LV (FOLFOX4), has demonstrated superiority over oxaliplatin/CPT-11 (IROX) or CPT-11/5-FU/LV (Saltz) in terms of the toxicity profile.[26,27] In this regard, the response rate of 39%, with a lower incidence of diarrhea and nausea/vomiting with our modified Saltz regimen, is encouraging, and appears to be comparable to findings reported in the FOLFOX4 study.[27] A multicenter phase II study of our regimen is currently underway.

## References


1. Jonker DJ, Maroun JA, Kocha W (2000) Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. Br J Cancer 82:1789–1794
2. Erlichman C, Fine S, Wong A, et al. (1988) A randomized trial of fluorouracil and folinic acid in patients with metastatic colorectal carcinoma. J Clin Oncol 6:469–475
3. Poon MA, O'Connell MJ, Moertel CG, et al. (1989) Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7:1407–1418
4. Pinedo HM, Peters GF (1988) Fluorouracil: biochemistry and pharmacology. J Clin Oncol 6:1653–1664
5. Poon MA, O'Connell MJ, Wieand HS, et al. (1991) Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. J Clin Oncol 9:1967–1972
6. Borner MM, Castiglione M, Bacchi M, et al. (1998) The impact of adding low-dose leucovorin to monthly 5-fluorouracil in advanced colorectal carcinoma: results of a phase III trial. Swiss Group for Clinical Cancer Research (SAKK). Ann Oncol 9:535–541
7. Buroker TR, O'Connell MJ, Wieand HS, et al. (1994) Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. J Clin Oncol 12:14–20
8. Hsiang YH, Lihou MG, Liu LF (1989) Arrest of replication forks by drug-stabilized topoisomerase I-DNA cleavable complexes as a mechanism of cell killing by camptothecin. Cancer Res 49:5077–5082
9. Kawato Y, Aonuma M, Hirota Y, et al. (1991) Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. Cancer Res 51:4187–4191
10. Shimada Y, Yoshino M, Wakui A, et al. (1993) Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. CPT-11 Gastrointestinal Cancer Study Group. J Clin Oncol 11:909–913
11. Conti JA, Kemeny NE, Saltz LB, et al. (1996) Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. J Clin Oncol 14:709–715
12. Pitot HC, Wender DB, O'Connell MJ, et al. (1997) Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. J Clin Oncol 15:2910–2919
13. Rougier P, Bugat R, Douillard JY, et al. (1997) Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol 15:251–260

14. Cunningham D, Pyrhonen S, James RD, et al. (1998) Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413–1418
15. Rothenberg ML, Cox JV, DeVore RF, et al. (1999) A multicenter, phase II trial of weekly irinotecan (CPT-11) in patients with previously treated colorectal carcinoma. Cancer 85:786–795
16. Pavillard V, Formento P, et al. (1998) Combination of irinotecan (CPT-1111) and 5-fluorouracil with an analysis of cellular determinants of drug activity. Biochem Pharmacol 56:1315–1322
17. Mullany S, Svingen PA, Kaufmann SH, et al. (1998) Effect of adding the topoisomerase I poison 7-ethyl-10-hydroxy-camptothecin (SN-38) to 5-fluorouracil and folinic acid in HCT-8 cells: elevated dTTP pools and enhanced cytotoxicity. Cancer Chemother Pharmacol 42:391–399
18. Saltz LB, Cox JV, Blanke C, et al. (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 343:905–914
19. Douillard JY, Cunningham D, Roth AD, et al. (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355:1041–1047
20. Rothenberg ML, Meropol NJ, Poplin EA, et al. (2001) Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 19:3801–3807
21. Sargent DJ, Niedzwiecki D, O'Connell MJ, et al. (2001) Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. N Engl J Med 345:144–145
22. Bertrand R, Jolivet J (1989) Lack of interference by the unnatural isomer of 5-formyltetrahydrofolate with the effects of the natural isomer in leucovorin preparations. J Natl Cancer Inst 81:1175–1178
23. Scheithauer W, Kornek G, Marczell A, et al. (1997) Fluorouracil plus racemic leucovorin versus fluorouracil combined with the pure *l*-isomer of leucovorin for the treatment of advanced colorectal cancer: a randomized phase III study. J Clin Oncol 15:908–914
24. Goldberg RM, Hatfield AK, Kahn M, et al. (1997) Prospectively randomized North Central Cancer Treatment Group trial of intensive-course fluorouracil combined with the *l*-isomer of intravenous leucovorin, oral leucovorin, or intravenous leucovorin for the treatment of advanced colorectal cancer. J Clin Oncol 15:3320–3329
25. Wasserman E, Sutherland W, Cvitkovic E (2001) Irinotecan plus oxaliplatin: a promising combination for advanced colorectal cancer. Clin Colorectal Cancer 1:149–153
26. Goldberg RM, Morton RF, Sargent DJ, et al. (2002) N9741: oxaliplatin or CPT-11 + 5-fluorouracil/leucovorin or oxaliplatin + CPT-11 in advanced colorectal cancer. Initial toxicity and response data from a GI Intergroup study (abstract). Proc Am Soc Clin Oncol 21:128
27. Goldberg RM, Morton RF, Sargent DJ, et al. (2003). N9741: oxaliplatin (Oxal) or CPT-11 + 5-fluorouracil/leucovorin or Oxal + CTP-11 in advanced colorectal cancer. Updated efficacy and quality of life data from an intergroup study (abstract). Proc Am Soc Clin Oncol 22:1009