Cancer Chemother Pharmacol (2003) 52: 125–130
DOI 10.1007/s00280-003-0604-1

ORIGINAL ARTICLE

**Yasuhide Yamada · Kuniaki Shirao
Ichinosuke Hyodo · Yasuaki Arai
Tadamichi Denda · Tomonori Ambo · Atsushi Ohtsu**

Phase II study of biweekly irinotecan and mitomycin C combination therapy in patients with fluoropyrimidine-resistant advanced colorectal cancer

Received: 26 September 2002 / Accepted: 13 February 2003 / Published online: 29 May 2003

Abstract *Purpose*: Experimental studies have shown that mitomycin C (MMC) acts synergistically with irinotecan. We evaluated the antitumor activity and toxicity of a combination of irinotecan and MMC in patients with metastatic colorectal cancer resistant to fluoropyrimidines. *Methods*: Eligible patients had evidence of tumor progression while receiving fluoropyrimidine-based regimens or had disease recurrence within 6 months after the completion of adjuvant treatment with fluoropyrimidines. Irinotecan (150 mg/m^2) and MMC (5 mg/m^2) were administered on days 1 and 15 of a 28-day cycle. Treatment was repeated every 4 weeks. *Results*: Among the 41 patients enrolled, 37 (90%) had received previous chemotherapy for metastatic disease, and 4 had received adjuvant chemotherapy alone. Objective responses were observed in 14 patients (34%, 95% confidence interval 20–49%). The median time to progression was 4.2 months, and the median survival time was 11.9 months. The study treatment was well tolerated; the median number of cycles received was four. Grade 3 or 4 neutropenia, the most common toxic effect, occurred in 20 patients (49%). Grade 3 or 4 thrombocytopenia occurred in four patients (10%) and grade 3 diarrhea in one patient. *Conclusions*: Our results suggest that irinotecan and MMC combination therapy is effective and well tolerated in patients with fluoropyrimidine-resistant metastatic colorectal cancer. Further clinical investigation of this regimen is warranted.

Keywords Colorectal cancer · 5-Fluorouracil · Irinotecan · Mitomycin C · Phase II study · Refractory

Y. Yamada (✉) · K. Shirao
Division of Gastrointestinal Oncology,
National Cancer Center Hospital, Tokyo, Japan
E-mail: yayamada@ncc.go.jp
Tel.: +81-3-35422511
Fax: +81-3-35423815

I. Hyodo
Department of Internal Medicine,
National Shikoku Cancer Center, Matsuyama, Japan

Y. Arai
Department of Diagnostic Radiology,
Aichi Cancer Center, Nagoya, Japan

T. Denda
Division of Hematology/Oncology,
Chiba Cancer Center Hospital, Chiba, Japan

T. Ambo
Department of Gastroenterology,
Sapporo Kosei General Hospital, Sapporo, Japan

A. Ohtsu
Division of Gastrointestinal Oncology/Digestive Endoscopy,
National Cancer Center Hospital East, Kashiwa, Japan

Y. Yamada
Division of Gastrointestinal Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, 104-0045, Tokyo, Japan

Introduction

The standard first-line therapy for advanced colorectal cancer for two decades, 5-fluorouracil (5-FU) with leucovorin (LV), has a response rate of only 23% and a median survival time (MST) of 11.5 months [17]. Irinotecan is a potent inhibitor of topoisomerase I. In randomized phase III trials, irinotecan prolonged survival significantly as compared with best supportive care or infusional 5-FU as a second-line therapy [4, 14]. Two other randomized phase III trials have shown that a combination of irinotecan, 5-FU, and LV is associated with higher response rates, a longer time to progression (TTP), and longer overall survival than 5-FU/LV therapy [5, 15]. The MST in patients given this three-drug therapy ranged from 14.8 to 17.4 months. Oxaliplatin (L-OHP), a diaminocyclohexane platinum complex, is also active against metastatic colorectal cancer. In phase II trials, objective response rates were 20% in chemotherapy-naive patients and 10% in previously treated patients [1, 10]. In a recent randomized phase III trial, the MST was 18.6 months with L-OHP/5-FU/LV, 14.1 months with irinotecan/5-FU/LV, and 16.5 months

with L-OHP/irinotecan [8]. L-OHP/5-FU/LV therapy thus holds promise of becoming a first-line treatment for metastatic colorectal cancer.

Mitomycin C (MMC) has also been demonstrated to be effective against metastatic colorectal cancer [3, 12]. A combination of protracted venous infusion (PVI) 5-FU and MMC in chemotherapy-naive patients results in a higher response rate and longer TTP than PVI 5-FU alone (response rate 54% vs 38%, median TTP 7.9 months vs 5.4 months) [12]. The MST is similar (14 months vs 15 months). When used as a second-line treatment for patients with colorectal cancer refractory to bolus 5-FU/LV, PVI 5-FU and MMC show modest activity with acceptable toxicity [3]. The response rate was 17%, and the MST 11.5 months. Preclinical studies have shown that a combination of MMC and irinotecan synergistically inhibits tumor growth in vitro [9, 21]. MMC may induce topoisomerase I gene expression, thereby increasing the sensitivity of tumor cells to irinotecan [21]. A phase I/II study of this combination has shown promising activity in patients with advanced gastric cancer. The study was designed to determine the recommended doses in an every 2-week schedule [23]. The maximum tolerated dose was 150 mg/m^2 of irinotecan plus 10 mg/m^2 of MMC administered on days 1 and 15 of a 28-day cycle. All patients receiving this dosage had grade 4 neutropenia. A combination of irinotecan 150 mg/m^2 and MMC 5 mg/m^2 was therefore used in subsequent phase II trials. The overall response rate was 50% (15/30 patients), and 5 of 14 patients (36%) who had received prior chemotherapy had a partial response (PR). In another phase II trial, the response rate with irinotecan alone was 16% in previously treated patients who had advanced gastric cancer [7]. Prior studies have thus shown that MMC enhances the response to 5-FU in colorectal cancer and irinotecan in gastric cancer.

In this phase II trial the antitumor activity and toxicity of combination therapy with irinotecan and MMC were evaluated in patients with metastatic colorectal cancer refractory to 5-FU. A key goal was to determine whether this combination of drugs was likely to be more effective than irinotecan monotherapy.

Patients and methods

Patient eligibility

To be eligible, patients had to have histologically confirmed and measurable colorectal cancer and to have previously received fluoropyrimidines. Patients given fluoropyrimidines for metastatic disease had to have evidence of tumor progression. Patients who had received adjuvant chemotherapy with fluoropyrimidines were eligible if they had disease recurrence within 6 months after the completion of such therapy. There was no restriction on prior radiotherapy, except that at least 4 weeks had to have elapsed between the completion of radiotherapy and study entry. In addition, patients had to be between 20 and 75 years of age, have an Eastern Cooperative Group (ECOG) performance status of 0 to 2, and meet the following criteria: a baseline bone marrow white blood cell (WBC) count and platelet count of more than 4000/μl and 100,000/μl, respectively; adequate hepatic levels of serum bilirubin, and serum aspartate aminotransferase and alanine aminotransferase levels of 2.0 mg/dl or less and 100 U/l or less, respectively; adequate renal function (blood urea nitrogen and serum creatinine levels of 25 mg/dl or less and 1.5 mg/dl or less, respectively); adequate respiratory function (arterial partial pressure of oxygen 70 mmHg or higher); and a life expectancy of at least 8 weeks.

Patients were excluded if they had symptomatic brain metastasis, previously received pelvic irradiation, previously received chemotherapy with irinotecan or MMC, pre-existing diarrhea, or a high risk of a poor outcome due to concomitant nonmalignant disease (cardiac, pulmonary, renal, or hepatic disease, or uncontrolled infection). This study was approved by the institutional review boards of each participating hospital. All patients gave written informed consent.

Before enrollment, all patients underwent a physical examination, complete blood cell count with differential count, serum chemical analysis, chest radiography, electrocardiogram, and computed tomographic (CT) scanning or magnetic resonance imaging (MRI).

Treatment plan

Eight centers in Japan participated in this study. MMC (5 mg/m^2) was dissolved in 20 ml normal saline and was given by bolus injection on days 1 and 15 of a 28-day cycle. Irinotecan (150 mg/m^2) was diluted in 250 ml 5% glucose solution and administered as a 90-min intravenous infusion on the same day, starting immediately after treatment with MMC. All patients were treated on an outpatient basis and received premedication with a 5-hydroxytryptamine-3-receptor antagonist, dexamethasone, or both. Treatment cycles were repeated, and response assessed every 4 weeks. Subsequent cycles of treatment were withheld until the WBC count and platelet count were greater than 3000/μl and 100,000/μl, respectively. Treatment was repeated until the onset of disease progression or severe toxicity. The maximum total dose of MMC had to be 50 mg/m^2 or less in each patient to prevent delayed cumulative toxicity, such as interstitial pneumonitis and hemolytic uremic syndrome. Patients who had no evidence of tumor progression after receiving the maximum dose of MMC were subsequently given irinotecan alone.

The dose was modified for each patient according to a nomogram based on hematologic or non-hematologic toxicity. If the nadir WBC count was <500/μl or the nadir platelet count was $<10{,}000$/μl, the subsequent dose of irinotecan was reduced to 125 mg/m^2. If the WBC count on day 15 was <3000/μl or the platelet count $<100{,}000$/μl, further treatment was delayed for a maximum of 2 weeks until recovery. Recombinant granulocyte colony-stimulating factor was administered subcutaneously to patients who had a WBC count of <1000/μl or a neutrophil count <500/μl for more than 5 days, and those who had neutropenic fever, but was not routinely used. If diarrhea of grade 3 or 4 developed, the subsequent dose of irinotecan was reduced to 125 mg/m^2.

Response and toxicity criteria

The response of measurable and evaluable disease sites was assessed according to RECIST [18]. Tumor measurement was assessed by CT scan or MRI after every treatment cycle. PR was defined as more than a 30% decrease in the sum of the products of the greatest perpendicular diameters of measurable lesions, without development of any new lesions. No change (NC) was defined as a steady state of response less than a PR or as progression of less than 20% over the course of at least 4 weeks. Progressive disease (PD) was defined as an unequivocal increase of at least 20% in the sum of the products of the greatest perpendicular diameters of individual lesions. The appearance of clinically significant new lesions also constituted PD. Toxicity was assessed according to the

Table 1 Patient characteristics at baseline

Gender	
Male	19
Female	22
Age (years)	
Median	60
Range	28–74
Performance status	
0	29
1	11
2	1
Prior chemotherapy with fluoropyrimidines	
One regimen	28
Two regimens or more	9
Adjuvant alone	4
Sites of metastases	
Liver	24
Lung	22
Lymph nodes	10
Peritoneum	4
Bone	2
Others	3

National Cancer Institute Common Toxicity Criteria, version 2.0. During the study, all patients were evaluated on a biweekly basis for symptoms of toxicity. Complete blood cell counts including differential count, liver function tests, measurement of urea nitrogen, creatinine, and electrolyte levels and urinalysis were performed biweekly. Tumor size was assessed every 4 weeks. Treatment responses were confirmed by an independent review committee every 4 months.

Statistical methods

The required sample size for this study was calculated based on a target response rate of 40% and a minimum response rate of 20%, with an α error of 0.1 and a β error of 0.1. The required number of patients was estimated to be 40.

Overall survival was measured from the start of irinotecan and MMC therapy to the date of death from any cause. The Kaplan-Meier method was used to plot overall survival curves. Survival time was taken as the last follow-up date the patient was alive. The TTP was calculated from the initiation of therapy to the date of disease progression as assessed by the investigators.

Results

Patient characteristics

Between 5 April and 15 December 2000, 41 patients were enrolled at eight centers in Japan. All enrolled patients were treated with irinotecan and MMC. A total of 138 cycles were given. Response and toxicity were evaluated in all patients on an intent-to-treat basis. The baseline characteristics of the subjects are listed in Table 1. Of the 41 patients, 40 had a good performance status (0 or 1). Four patients had received adjuvant chemotherapy alone within 6 months before the start of treatment, and 37 patients had received prior chemotherapy for metastatic disease, either with or without adjuvant chemotherapy. In 18 of the 24 patients with liver metastasis, the tumor involved more than 25% of their liver parenchyma.

Table 2 Response

	No. of patients (%)
Assessable for response	41
Objective response	
Partial response	14 (34%)[a]
Confirmed partial response	13 (32)
Stabel disease	23 (56)
Progressive disease	4 (10)

[a]95% CI 20–49%

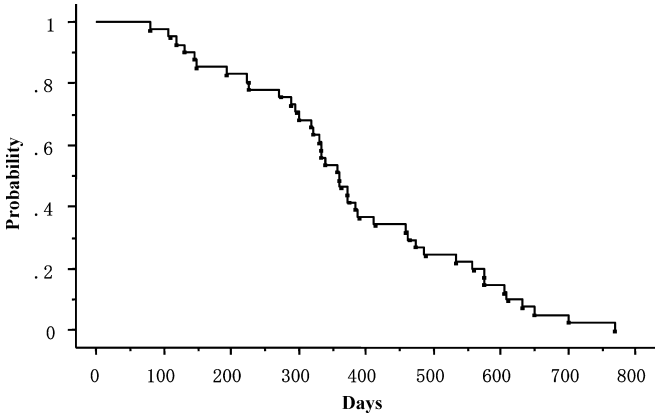

Fig. 1 Survival curve

Response and survival

The response results are summarized in Table 2. Fourteen patients had a PR, for an overall response rate of 34% (95% CI 20–49%). The median TTP was 4.2 months (range 1.0–11.9 months) and the MST was 12.0 months (range 2.7–25.3 months). The response rate was 38% (14/37) in patients who had received prior chemotherapy for metastatic disease and 0% (0/4) in those who had received adjuvant chemotherapy alone. The Kaplan-Meier survival curve is presented in Fig 1.

Toxicity

The WBC, neutrophil, and platelet counts of all patients were within normal limits at the start of treatment with irinotecan and MMC, as required by the study protocol. Hematologic toxicities according to the worst grade per patient for all treatment cycles are summarized in Table 3. Neutropenia was the most common and serious toxic effect: 20 of the 41 patients (49%) had grade 3 or 4 neutropenia, including 7 (17%) in whom febrile neutropenia developed. Grade 3 or 4 neutropenia occurred in 29% of the patients (12/41) during the first cycle of treatment. Grade 3 or 4 thrombocytopenia developed in only 10% of the patients (4/41) and the incidence during the first treatment cycle was 5%.

Table 3 Hematologic toxicities

	Grade 1–4	Grade 3/4
Leukopenia	35 (85%)	12 (29%)
Neutropenia	37 (90%)	20 (49%)
Anemia	24 (59%)	2 (5%)
Thrombocytopenia	12 (29%)	4 (10%)

Table 4 Non-hematologic toxicities

	Grade 1–4	Grade 3/4	Grade 5
Nausea	34 (83%)	5 (12%)	
Vomiting	16 (39%)	1 (2%)	
Diarrhea	24 (59%)	1 (2%)	
Fatigue	34 (83%)	6 (15%)	
Alopecia	38 (93%)		
Stomatitis	5 (12%)		
Infection without neutropenia	5 (12%)	1 (2%)	
Abdominal pain	3 (7%)		
Pneumonitis	1 (2%)		1 (2%)

Non-hematologic toxicities are shown in Table 4. Grade 3 delayed diarrhea occurred in one patient and was successfully managed with loperamide. One patient had drug-induced fatal interstitial pneumonitis after three cycles. The cumulative dose of MMC in this patient was 30 mg/m^2.

Treatment was delayed for 1 week at least one time in 16 of the 41 patients (39%; nine neutropenia, three fatigue, one diarrhea, one infection without neutropenia, one abdominal pain, one personal reasons). The dose of irinotecan was reduced to 125 mg/m^2 according to the study protocol in eight patients (22%; seven neutropenia, one diarrhea). The median number of treatment cycles was four (range one to five), and the total number of cycles was 138. The mean dose intensity was 125 mg/m^2 per 2 weeks for irinotecan and 4.2 mg/m^2 per 2 weeks for MMC.

Discussion

In this study, the effectiveness and safety of irinotecan and MMC therapy were assessed in patients with metastatic colorectal cancer refractory to 5-FU. The overall response rate was 34%, and the MST was 12 months. Hematologic toxicity was tolerable, and treatment could be administered on an outpatient basis. Grade 3 or 4 neutropenia was the most common toxicity, occurring in 49% of the study group when assessed according to the worst grade per patient among all cycles. Febrile neutropenia developed in 17% of patients. Our results suggest that combination therapy with irinotecan and MMC is effective and safe for the treatment of metastatic colorectal cancer.

The response rate with irinotecan alone in patients who have colorectal cancer previously treated with 5-FU ranges from 14% to 18%, with a MST of 9.2 to 10.8 months [4, 13, 14]. Comella et al. performed a phase I/II trial of irinotecan and MMC therapy in patients with 5-FU-refractory colorectal [2]. Irinotecan 175 mg/m^2 was administered on days 1 and 8, and MMC 10 mg/m^2 was given on day 1 of a 28-day cycle. The response rate was 12% (5/40), and the MST was 14.5 months. Grade 3 or 4 neutropenia as defined by the World Health Organization (WHO) [22] developed in 26% of the patients. Although this regimen was modestly effective, the potential benefits of MMC were uncertain. Scheithauer et al. reported a phase II trial of irinotecan and MMC in patients with 5-FU/LV-pretreated colorectal cancer [16]. Irinotecan 120 mg/m^2 was given on days 1 and 15 and MMC 8 mg/m^2 was administered on day 1. The response rate was 21% (7/33), and the MST 12 months. WHO grade 3 or 4 neutropenia occurred in 33% of the patients. There are limitations in comparing data derived from different studies. Nevertheless, we found that biweekly treatment with irinotecan and MMC therapy produced a higher response rate than previously used regimens. The MST in our study was 12 months, similar or slightly superior to that reported for irinotecan alone.

The administration schedule of irinotecan and MMC in this study differed from that used in previous studies. Both drugs were given on days 1 and 15 of a 28-day cycle. Phase I studies of these drugs have shown that MMC induces topoisomerase I gene expression and enhances the antitumor activity of irinotecan [21]. MMC may modulate the activity of irinotecan by upregulating topoisomerase I.

As well as enhancing antitumor activity, this mechanism may have contributed to the higher incidence of grade 3 or 4 neutropenia than that reported for other treatment schedules. Unlike previous studies, we gave irinotecan immediately after MMC on the same days. The first-line standard treatment for colorectal cancer is currently irinotecan/5-FU/LV therapy or L-OHP/5-FU/LV therapy. In addition, a phase III trial comparing a combination of irinotecan/5-FU/LV with sequential treatment with 5-FU/LV followed by irinotecan is ongoing. Because only 30% to 40% of the patients received 5-FU/LV followed by irinotecan in previous phase III trials [5, 15], the response to this regimen should be confirmed in randomized phase III studies versus irinotecan alone in patients with colorectal cancer refractory to 5-FU or L-OHP/5-FU.

The median dose intensity was 125 mg/m^2 per 2 weeks for irinotecan and 4.2 mg/m^2 per 2 weeks for MMC. Most patients received both drugs at 80% of the doses required by the study protocol every 2 weeks. The most common adverse reaction was grade 3 or 4 neutropenia, which occurred in 49% of the patients in the study. After the first cycle of therapy, the incidence of grade 3 and 4 neutropenia was 29%. The incidence of neutropenia increased subsequently. This high frequency of neutropenia suggests that the dose should be decreased to 125 mg/m^2 of irinotecan and 4 mg/m^2 of MMC. Grade 3 or 4 non-hematologic toxicity included

fatigue (15%) and nausea (12%). Grade 3 diarrhea occurred in only one patient. Gastrointestinal toxicity was well controlled by treatment with antiemetic agents, dexamethasone, and loperamide. One patient had fatal interstitial pneumonitis after receiving a cumulative dose of 30 mg/m^2 of MMC. Although this patient received a high dose of corticosteroids, respiratory failure progressed rapidly. The incidence of pulmonary toxicity with MMC is approximately 7% and rises when the cumulative dose exceeds 30 mg/m^2 [19, 20]. Irinotecan-associated interstitial pneumonitis has also been reported [6, 11]. The incidence of pulmonary toxicity due to irinotecan was 3% in a phase II trial of patients with non-small-cell lung cancer. Patients treated with irinotecan and MMC should thus be closely observed for pulmonary toxicity. Hemolytic uremic syndrome did not occur in our study.

In conclusion, our study showed that biweekly irinotecan and MMC combination therapy is a tolerated and active regimen in patients with advanced colorectal cancer resistant to fluoropyrimidine chemotherapy. We believe that further studies of this combination therapy are warranted in patients with colorectal cancer refractory to 5-FU/LV or L-OHP/5-FU/LV.

Acknowledgements This study was supported by a Grant-in-Aid for Cancer Research from the Ministry of Health, Welfare and Labor, Japan. The following centers participated in the study: Medical Oncology Division, National Cancer Center Hospital (Y. Matsumura, K. Muro, M. Goto); Department of Internal Medicine, National Shikoku Cancer Center Hospital (T. Nishina); Department of Internal Medicine, Chiba Cancer Center (T. Takagi, T. Saotome); Department of Internal Medicine, Sapporo Kosei Hospital (A. Imamura); Third Department of Internal Medicine, Hokkaido University School of Medicine (A. Masahiro, Y. Komatsu); Department of Internal Medicine, Aomori Prefectural Central Hospital (S. Saito); and Department of Internal Medicine, Saku General Hospital (Y. Miyata).

References

1. Becouarn Y, Ychou M, Ducreaux M, Borel C, Bertheault-Cvitkovic F, Seitz JF, Nasca S, Nguyen TD, Paillot B, Raoul JL, Duffour J, Fandi A, Dupont-Andre G, Rougier P (1998) Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. J Clin Oncol 16:2739–2744
2. Comella P, Biglietto M, Casaretti R, De Lucia L, Avallone A, Maiorino L, Di Lullo L, De Cataldis G, Rivellini F, Comella G (2001) Irinotecan and mitomycin C in 5-fluorouracil-refractory colorectal cancer patients. Oncology 60:127–133
3. Conti JA, Kemeny NE, Saltz LB, Andre AM, Grossano DD, Bertino JR (1995) Continuous infusion fluorouracil/leucovorin and bolus mitomycin-C as a salvage regimen for patients with advanced colorectal cancer. Cancer 75:769–774
4. Cunningham D, Pyrhonen S, James RD, Punt CJA, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C, Herait P (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
5. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Grucia G, Awad L, Rougier P (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
6. Fukuoka M, Niitani H, Suzuki A, Motomiya M, Hasegawa K, Nishiwaki Y, Kuriyama T, Ariyoshi Y, Negoro S, Masuda N (1992) A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol 10:16–20
7. Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, Yoshino M, Taguchi T, Ogawa N (1994) Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. CPT-11 Gastrointestinal Cancer Study Group. Jpn J Cancer Chemother 21:1033–1038
8. Goldberg RM, Morton RF, Sargent DJ, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP (2002) N9741: oxaliplatin (oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer. Initial toxicity and response data from a GI Intergroup Study. Proc ASCO 21:511
9. Kano Y, Suzuki K, Akutsu M, Suda K, Inoue Y, Yoshida M, Sakamoto S, Miura Y (1992) Effects of CPT-11 in combination with other anti-cancer agents in culture. Int J Cancer 50:604–610
10. 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 (1996) 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 7:95–98
11. Madarnas Y, Wbster P, Shorter AM, Bjarnason GA (2000) Irinotecan-associated pulmonary toxicity. Anticancer Drugs 11:709–713
12. Ross P, Norman A, Cunningham D, Webb A, Iveson T, Padhani A, Prendiville J, Watson M, Massey A, Popescu R, Oates J (1997) A prospective randomized trial of protracted venous infusion 5-fluorouracil with or without mitomycin C in advanced colorectal cancer. Ann Oncol 8:995–1001
13. Rougier P, Bugat R, Douillard JY, Culine S, Suc E, Brunet P, Becouarn Y, Ychou M, Marty M, Extra JM, Bonneterre J, Adenis A, Seitz JF, Ganem G, Namer M, Conroy T, Negrier S, Merrouche Y, Burki F, Mousseau M, Herait P, Mahjoubi M (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. 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 (1998) Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407–1412
15. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343:905–914
16. Scheithauer W, Kornek GV, Brugger S, Ullrich-Pur H, Valencak J, Raderer M, Fiebiger W, Kovats E, Lang F, Depisch D (2002) Randomized phase II study of irinotecan plus mitomycin C vs. oxaliplatin plus mitomycin C in patients with advanced fluoropyrimidine/leucovorin-pretreated colorectal cancer. Cancer Invest 20:60–68
17. The Advanced Colorectal Cancer Meta-Analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10:896–903
18. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216

19. Verweij J, Van Zanten T, Souren T, Golding R, Pinedo HM (1987) Prospective study on the dose relationship of mitomycin C-induced interstitial pneumonitis. Cancer 60:756–761
20. Verweij J, Den Hartigh J, Pinedo HM (1990) Antitumor antibiotics. In: Chabner B, Collins JM (eds) Cancer chemotherapy—principles and practice. Lippincott, Philadelphia, p 382
21. Villalona-Calero MA, Kuhn J, Drengler R, Schaaf L, Otterson GA, Shapiro C, Thurman A, Diab S, Hammond L, Von Hoff D, Felton S, Hauger M, Monroe P, Rowinsky E, Kolesar J (2001) Pharmacologically-based phase I study of mitomycin-C as a modulator of irinotecan antitumor activity. Proc ASCO 20:400
22. World Health Organization (1970) Handbook for reporting results of cancer treatment (official publication no. 48). World Health Organization, Geneva
23. Yamao T, Shirao K, Matsumura Y, Muro K, Yamada Y, Goto M, Chin K, Shimada Y (2001) Phase I-II study of irinotecan combined with mitomycin-C in patients with advanced gastric cancer. Ann Oncol 12:1729–1735