Prospective multicenter phase II study of irinotecan as third-line therapy in metastatic colorectal cancer and progression after bolus and infusional 5-fluorouracil

Joerg Thomas Hartmann[a], Karin Oechsle[a], Elke Jäger[b], Hans Edgar Reis[c], Cornelie Haag[d], Norbert Niederle[e], Hans-Joachim Wilke[f], Karl-Heinz Pflüger[g], Salah Al Batran[b], Thomas Büchele[h], Ralf D. Hofheinz[i], Lothar Kanz[a] and Carsten Bokemeyer[a]

Irinotecan has proven anti-tumor activity as induction treatment in combination with 5-fluorouracil (5-FU) or as second-line treatment after 5-FU in patients with metastatic colorectal cancer. The aim of the present phase II study was to evaluate irinotecan as third-line chemotherapy in patients with colorectal cancer after sequential treatment with bolus 5-FU followed by an infusional 5-FU regimen. Patients pretreated with bolus 5-FU/folinic acid and the infusional 5-FU/folinic acid regimen were treated with 350 mg/m^2 irinotecan i.v. once every 3 weeks in a multicenter phase II study. Tumor size was measured every cycle and treatment with irinotecan was continued until the occurrence of progressive disease or unacceptable toxicity. A total of 50 pretreated patients were included. Of the 45 evaluable patients, 13.3% [*n* = 6, 95% confidence interval (CI) 5.1–26.8] attained a response (complete/partial response) to treatment lasting 5.6 months (95% CI 4.2–6.3) and in four patients response has been confirmed (8.9%, 95% CI 2.5–21.2). Disease stabilization was noted in 51.1% of the patients (*n* = 23, 95% CI 35.8–66.3). The median duration of response/disease stabilization was 4.2 months (95% CI 3.2–6.0). Median overall survival was 7.9 months (95% CI 6.1–11.1), corresponding to a calculated 1-year survival of 28.3% (95% CI 15.2–41.3). Severe neutropenia occurred in 14% (*n* = 7) and anemia grade III in 6% of the patients (*n* = 3). The most frequent non-hematological toxicity grade III/IV related to treatment was diarrhea in 24% of the patients (*n* = 12), followed by vomiting in 8% (*n* = 4) and constipation as well as infection in two patients each (4%) (evaluable *n* = 50). We conclude single-agent irinotecan is an effective and well-tolerable treatment in pretreated patients with metastatic colorectal cancer after failure of bolus and infusional 5-FU/folinic acid regimens. Elderly patients had the same probability to respond. *Anti-Cancer Drugs* 15:473–477 © 2004 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2004, **15**:473–477

Keywords: metastatic colorectal cancer, irinotecan, phase II, third-line chemotherapy

[a]Abt. Hämatologie/Onkologie/Immunologie/Rheumatologie, Medizinische Klinik II, Eberhard-Karls-Universität, Tübingen, Germany, [b]Krankenhaus Nordwest, Frankfurt, Germany, [c]Kliniken Maria Hilf, Mönchengladbach, Germany, [d]Medizinische Klinik I, Universitätsklinikum Dresden, Dresden, Germany, [e]Klinikum Leverkusen, Leverkusen, Germany, [f]Kliniken Essen Mitte, Essen, Germany, [g]Ev. Diakoniekrankenhaus, Bremen, Germany, [h]Aventis Pharma, Bad Soden, Germany and [i]Medizinische Klinik III, Klinikum Mannheim, Mannheim, Germany.

Correspondence to J. T. Hartmann, Department of Hematology/Oncology/Immunology/Rheumatology, UKT Medical Center II, Eberhard-Karls-University Tübingen, Otfried-Mueller-Strasse 10, 72076 Tübingen, Germany.
Tel: +49 7071 29 82127 or 82125; fax: +49 7071 29 5689;
e-mail: joerg.hartmann@med.uni-tuebingen.de

Received 20 January 2004 **Revised form accepted** 10 February 2004

Introduction

Metastatic colorectal cancer is a major cause of cancer-related mortality. The majority of patients require the consideration of systemic chemotherapy as palliative treatment for their diseases. The use of new effective chemotherapy agents such as irinotecan (CPT-11) and oxaliplatin has resulted in a clinically significant improvement in survival for patients with metastatic colorectal cancer. Randomized trials in the first-line setting in which patients were likely to have access to all effective drugs demonstrated a median survival of 18–20 months [1]. This compares favorably to survival data of approximately 11–13 months for patients treated with bolus or infusional 5-fluorouracil (5-FU)/folinic acid regimens alone [2]. Irinotecan hydrochloride trihydrate (irinotecan/CPT-11), a semisynthetic derivate of camptothecin, has demonstrated a significant activity in colorectal cancer patients [3]. In first-line use, single-agent activity of irinotecan was the same as the standard folinic acid-modulated 5-FU monthly regimen [4]. The addition of irinotecan to 5-FU has been compared with modulated 5-FU in three randomized studies. All studies have reported a significantly higher response rate and a significantly longer time to progression for the combina-

0959-4973 © 2004 Lippincott Williams & Wilkins DOI: 10.1097/01.cad.0000127144.73043.57

tion arm [4–6]. In addition, two of these trials also demonstrated a substantial gain by the addition of irinotecan in terms of survival [4,5]. In addition, oxaliplatin has also demonstrated some activity as a single agent [7], but has been usually combined with modulated 5-FU due to marked synergistic effects [8]. In a randomized trial, a biweekly regimen of 5-FU plus oxaliplatin was compared with the same 5-FU infusion schedule without oxaliplatin and a significantly higher response rate as well as a significantly longer time to progression were reported in favor of the combination arm [9]. However, the optimal sequences and combinations of these agents as initial and salvage chemotherapy along with 5-FU and folinic acid are still controversial, and in clinical practice many patients are treated with sequential chemotherapy to avoid toxicity, particularly in the elderly population. The aim of the present multicenter phase II study was to evaluate the efficacy and the feasibility of single-agent irinotecan as third-line treatment after bolus 5-FU and continuous infusional 5-FU plus folinic acid in patients with metastatic colorectal cancer.

Patients and methods

Eligibility

Patients eligible for this open label non-randomized multicenter phase II study (AN 96021) had to have metastatic histologically confirmed adenocarcinoma of the colon or rectum, had received at least two prior chemotherapy regimens for metastatic disease, consisting of first-line treatment with a bolus regimen of 5-FU/folinic acid (400–425 mg/m^2 5-FU plus 20–200 mg/m^2 folinic acid i.v. day 1–5 or 500–600 mg/m^2 5-FU plus 200–500 mg/m^2 folinic acid i.v. weekly) and with continuous infusional 5-FU/folinic acid (2600 mg/m^2 5-FU over 24 h plus 500 mg/m^2 folinic acid i.v. weekly for 6 weeks). Objective evidence of tumor progression must have occurred while the patient was receiving chemotherapy or within 6 months from receiving the last dose of prior chemotherapy. The time between the start of study treatment and previous chemotherapy or radiation had to be at least 4 weeks. Adjuvant chemotherapy with one 5-FU-based regimen or radiotherapy may have been administrated.

Patients must have been between 18 and 75 years, have had a performance status of 0–2 according to the WHO criteria and a life expectancy of at least 3 months. Other inclusion criteria consisted of pretreatment neutrophil count $\geq$ 2000/μl, platelet count $\geq$ 100 000/μl, hemoglobin level $\geq$ 10 g/dl and serum creatinine concentration $\leq$ 140 μmol/l, respective creatinine clearance $\geq$ 60 ml/min. In the absence of liver metastases total serum bilirubin levels had to be $\leq 1.25 \times$ upper normal value of the institutional reference range, and ASAT (SGOT) and ALAT (SGPT) $\geq 3 \times$ upper normal value. In patients with hepatic metastases a total serum bilirubin of $\leq 1.5 \times$ upper normal value and ASAT/ALAT $\leq 5 \times$ upper normal value were allowed.

Patients were excluded if they had unresolved bowel obstruction or diarrhea, chronic diarrhea, presence of central nervous metastases, serious or uncontrolled concurrent medical illness, or secondary malignancies except for basalioma or carcinoma *in situ* of cervix uteri or other cancer curatively treated and with no evidence of disease for at least 5 years. Patients were further excluded with an involvement of the liver of more than 50% or more than 25% of the lung. Pregnant and lactating women were not included in the trial.

All patients were informed of the investigational nature of this study, and had to provide written informed consent in accordance with institutional and federal guidelines. The study was reviewed and approved by the local ethical committee. Treatment was performed according to the declaration of Helsinki on a multicenter basis.

Treatment protocol

Chemotherapy consisted of 350 mg/m^2 irinotecan given as an i.v. infusion over 30 min on day 1 once every 3 weeks. The total maximum dose of irinotecan was 700 mg even if the calculated body surface area was greater than 2 m^2. In patients aged over 70 years or patients with a WHO performance status of 2, treatment was started with a reduced dosage of 300 mg/m^2 irinotecan. Antiemetic premedication was left up to the decision of the treating physician in compliance with the conventional antiemetic protocol of the center for highly emetic substances.

Treatment was continued with the next cycle of irinotecan when neutrophil count had recovered to $\geq$ 2000/μl and platelet count to $\geq$ 100 000/μl, and all non-hematological toxicity had recovered to NCI grade I or baseline. If treatment had to be delayed for more than 2 weeks, the patient was taken off study. The irinotecan dose had to be reduced to 300 mg/m^2 (250 mg/m^2 in patients with 300 mg/m^2 starting dose) at the appearance of neutropenia or diarrhea grade IV according to the NCI criteria. No dose reduction below 250 mg/m^2 (or 200 mg/m^2 if starting dose was 300 mg/m^2) was allowed.

In the first cycle, no preventive medication for cholinergic syndrome and/or early diarrhea was administered. In case of occurrence of cholinergic syndrome or early diarrhea, 0.25 mg atropine s.c. was applied and was continued as prophylaxis before every further cycle. No prophylaxis for delayed diarrhea had to be given, especially no loperamide. Loperamide 2 mg p.o. every 2 h was started at the first occurrence of liquid stool, and continued for at least 12 h and up to 12 h after the last liquid stool occurred. Treatment duration did not exceed

48 h in total. Patients with diarrhea persisting for more than 24 h despite loperamide treatment received prophylactic oral, broad-spectrum antibiotics (e.g. quinolone antibiotics) for 7 days.

Evaluation of response and toxicity

All patients were assessed prior to treatment by physical examination, routine hematology, routine biochemistry and carcinoembryonal antigen (CEA) analysis, baseline toxicity evaluation, chest X-ray, ultrasound and CT scan, including the brain, to define the extent of disease. Complete blood cell counts with platelets and differential counts were obtained weekly during chemotherapy, and serum chemistry analyses were repeated at least once every course. Subjective symptoms, physical examination including weight and vital signs, performance status, and all adverse reactions were recorded before each treatment cycle. Biochemistry and CEA analysis as well as ECG were performed every 3 weeks. Tumor size was measured after every other treatment cycle by CT scan, X-ray or any other technique that allows retrospective and independent assessment. Determination of tumor response followed WHO standard criteria: complete remission (CR) was defined as a complete disappearance of all evidence of disease determined in two different observations within 4 weeks. A partial response (PR) was defined as radiological response above 50% in tumor size at two different observations 4 weeks apart. Response below 50% or progression above 25% was defined as stable disease. Progressive disease was defined as either residual lesions increasing in size or occurrence of new lesions [10].

Treatment was continued until the occurrence of progressive disease, unacceptable toxicity, treatment delays for more than 2 weeks, neutropenia or diarrhea grade IV despite two successive dose reductions, or withdrawal of consent. Patients were followed every 2 months after stopping treatment with irinotecan. Duration of response was defined as the interval from the onset of response until evidence of disease progression. Overall survival was defined as interval from date on study until death (or last contact if patient was still alive).

Study design and statistical analysis

The primary objective of the study was to determine the overall response rate (CR/PR) of irinotecan in advanced 5-FU-pretreated colorectal cancer. A two-stage study design was used [11]. With an α error of 5% and a power of 92%, the sample size was 20 patients for the first stage. The accrual was to stop if less than one remission was observed in the first 20 assessable patients.

Exact 95% confidence intervals (CI) around the observed response rate were calculated from the binominal distribution. The Kaplan–Meier method was used to determine overall and progression-free survival distributions. The overall survival calculation used death due to any reason as the endpoint [12].

Results

Patient characteristics

In total, 50 patients, 21 male and 29 female, were entered into this open label non-randomized multi-center phase II study. The median age was 59 years (range 39–77) and the median performance status according to the WHO criteria was 1 (range 0–2). All 50 patients were assessable for toxicity and survival analysis, and 45 were additionally assessable for response evaluation.

The primary tumor was located in the colon in 23 patients (46%), 25 patients (50%) had rectal cancer, and two patients (4%) had histologically proven synchronous adenocarcinoma in the colon and rectum. At the start of chemotherapy with irinotecan for metastatic disease, liver metastases were found in 88% of the patients ($n = 44$), metastases in the lungs in 42% ($n = 21$), abdominal lymph node involvement in 18% ($n = 9$), locoregional tumor progression in 16% ($n = 8$) and metastases in other locations in 8% of the patients ($n = 4$). In total, 24 patients (48%) had one single tumor location, 16 patients (32%) had two tumor locations and 10 patients (20%) had more than two different tumor sites. Seventy-six percent of the patients ($n = 38$) had been treated with the sequence bolus 5-FU–continuous infusion 5-FU or to lines of continuous infusion 5-FU prior to CPT-11. Five patients (10%) had received only one regimen consisting of continuous infusion 5-FU and seven patients (14%) had been treated with three regimen of 5-FU-based chemotherapy. The median interval between the last 5-FU regime and CPT-11 was 0 months (range 0–6) and 27 patients (54%) had progressive disease while receiving previous 5-FU regimen. Patient characteristics are given in Table 1.

Safety and toxicity assessment

In total, 216 cycles with a median of 4 (range 1–11) per patient were applied ($n = 50$ patients). Severe neutropenia (grade III/IV according to NCI criteria) occurred in 14% of the patients ($n = 7$). One of them (2%) experienced a febrile neutropenic infection not requiring hospitalization. Anemia grade III was seen in 6% of the patients ($n = 3$). The most frequent non-hematologic toxicity was diarrhea grade III/IV in 24% of the patients ($n = 12$); in five patients (10%) a grade IV was observed. Early cholinergic syndrome grade III during infusion of irinotecan occurred in four patients (8%). Other non-hematologic toxicities grade III/IV were rare: vomiting in 8% of the patients ($n = 4$), and constipation and infection in two patients each (4%). Serum biochemistry revealed reversible elevations of total bilirubin in 16% of patients ($n = 8$), alkaline phosphatase in 16% ($n = 8$) and lactate dehydrogenase (LDH) in 10% ($n = 5$), mostly related to

Table 1 Characteristics of patients with third-line treatment with irinotecan 350 mg/m^2 3-weekly after failure of bolus and infusional 5-FU (N=50)

	N	%
Median age [years (range)]	59 (39–77)	
Sex		
male	21	42
female	29	58
Performance status (WHO)		
0	20	40
1	28	56
2	2	4
Histology of primary tumor		
colon carcinoma	23	46
rectal carcinoma	25	50
colon + rectum	2	4
Sites of metastases		
liver	44	88
lymph nodes	9	18
lung	21	42
locoregional	8	16
peritoneal carcinosis	1	2
other sites	3	6
No. of prior chemotherapy regimen (for metastatic disease)		
1	5	10
2	38	76
3	7	14
Prior chemotherapy regimen		
bolus 5-FU/folinic acid alone	–	
c.i. 5-FU alone	5	10
sequence bolus–c.i.	33	66
sequence c.i.–c.i.	5	10
sequence bolus–bolus–c.i.	4	8
sequence bolus–c.i.–c.i.	3	6
adjuvant (bolus) chemotherapy	6	12

c.i. = continuous infusion.

tumor progression. The most important non-hematologic side-effects grade III/IV are summarized in Table 2. Overall, dose reductions of irinotecan due to toxicity were required in 10% of the patients (n = 8). In eight patients (16%), treatment was delayed for 1 week at least one time during chemotherapy due to medical reasons.

Response evaluation

Of the 45 evaluable patients, 13.3%. (n = 6, 95% CI 6.3–28.9) attained a PR to third-line treatment with irinotecan lasting for a median duration of 5.6 months (95% CI 4.2–6.3). In four patients, remissions could be confirmed at the second tumor assessment 4 weeks later (8.9%, 95% CI 2.5–21.2). In 51.1% of the patients (n = 26, 95% CI 35.8–71.1), best response was disease stabilization. The median duration of responses and disease stabilizations was 4.2 months (95% CI 3.2–6.0). Stabilizations alone lasted in median 3.3 months (95% CI 3.0–4.9). Sixteen patients (35.6%, 95% CI 21.9–51.2) had progressive disease at the first response evaluation. Time to progression was 3.0 months (95% CI 2.0–4.1). Elderly patients (aged over 65 years) had the same probability to attain a response to treatment (n = 15 patients, PR 13%; disease stabilization 33%) compared to younger patients. The median overall survival of 45 assessable was 7.9 months (95% CI 6.1–11.1) corresponding to a 1-year survival rate of 28.3% (95% CI 15.2–41.3).

Table 2 Worst toxicity grade III/IV (NCI) per patient during third-line treatment with irinotecan 350 mg/m^2 3-weekly for metastatic colorectal carcinoma (n=50 patients, n=216 cycles)

	Non-hematologic toxicities (NCI criteria) [*n* (%)]		
	Grade III	Grade IV	Grade III/IV
Diarrhea	7 (14)	5 (10)	12 (24)
Bilirubin elevation (total)	5 (10)	3 (6)	8 (16)
Neutropenia	2 (4)	5 (10)	7 (14)
Alkaline phosphatase	7 (14)	0	7 (14)
Pain	7 (14)	0	7 (14)
LDH	5 (10)	0	5 (10)
Cholinergic syndrome	4 (8)	0	4 (8)
Vomiting	1 (2)	3 (6)	4 (8)
Anemia	3 (6)	0	3 (6)
Infection	2 (4)	1 (2)	3 (6)
Constipation	2 (4)	0	2 (4)
Nausea	1 (2)	1 (2)	2 (4)
Asthenia	1 (2)	0	1 (2)
ALT	1 (2)	0	1 (2)
AST	1 (2)	0	1 (2)
Cardiac dysrhythmia	1 (2)	0	1 (2)
Cough	1 (2)	0	1 (2)
Mucositis	0	1 (2)	1 (2)
Serum creatinine	1 (2)	0	1 (2)

Discussion

This study aimed at determining the activity of CPT-11 as subsequent treatment after both bolus and continuous infusion 5-FU in patients with metastatic colorectal cancer. 5-FU has been the only important agent in the treatment of advanced colorectal cancer for more than 40 years. Single-agent activity of 5-FU is rather low with a remission rate of 10–15%. The modulation with folinic acid did not clearly prolong survival [2]. Second-line chemotherapy after 5-FU bolus application was given as infusional 5-FU and was offered for selected patients with good performance status [13,14]. Response rates from several phase II trials have been in the range of 10–15% and survival was 7–11 months. Results achieved with other drugs in this setting or in the first-line revealed only a modest efficacy in colorectal cancer patients [15,16]. With the introduction of irinotecan, a topoisomerase I inhibitor, another effective agent for the treatment of patients with metastatic colorectal cancer was available. Objective response rates of approximately 30% with median response durations of 5.6–11.5 months in patients with metastatic colorectal cancer as first-line treatment [4] and 14–23% with a survival duration of 9–11 months as second-line treatment after failure of 5-FU-based chemotherapy have been documented [17,18]. A randomized trial comparing irinotecan to continuous infusional 5-FU plus folinic acid as second-line treatment after bolus 5-FU failure demonstrated a survival advantage of 2.3 months (8.5 versus 10.8) [19]. Oxaliplatin was the third agent showing significant antitumor activity in patients with metastatic colorectal cancer [9,20] and therefore third-line treatment in colorectal cancer became realistic. However, decisions regarding the optimal approach for patients with metastatic disease have become more complex, and it is still an open question whether sequential use of effective drugs or

upfront combination regimens of 5-FU/folinic acid and either irinotecan or oxaliplatin should be employed. Data from two randomized phase III first-line trials seemed to indicate that combination chemotherapy is associated with a statistical significant survival advantage of 3 months [4,5]; however, recently published phase III investigations with access to all effective drugs revealed no statistical survival advantage for patients receiving upfront combination chemotherapy compared to 5-FU alone [6,21]. Despite the approval of new drugs for the first-line treatment of metastatic colorectal cancer, infusional 5-FU therapy alone and even 5-FU bolus regimen are still in use in clinical practice, particularly in elderly patients, which are not mostly excluded from controlled clinical trials due to age restriction or co-morbidity. Thus, the present investigation evaluated the efficacy and tolerability of irinotecan as third-line treatment after failure of both 5-FU schedules, first a bolus regimen and second a continuous infusional regimen plus folinic acid as an example for a sequential treatment regimen. With a remission rate of 13% lasting for 5.6 months (median) and disease stabilization in 51% of patients with a median duration of 3.3 months (95% CI 3.0-4.9), irinotecan showed significant antitumor activity in this third-line setting. The median overall survival was of 7.9 months (95% CI 6.1–11.1) and the calculated 1-year-survival was determined at 28.3% (95% CI 15.2–41.3). These results are comparable to the data achieved with irinotecan in the second-line setting [17,18].

In patients pretreated with two 5-FU regimens, 350 mg/m^2 of irinotecan every 3 weeks did not result in an elevated rate of severe neutropenia or diarrhea compared to second-line studies. Other non-hematological toxicities have been observed rarely.

In conclusion, irinotecan as a single agent given every third week at a dose of 350 mg/m^2 is a well-tolerated and effective regimen in patients with metastatic colorectal cancer after failure of the two 5-FU-based chemotherapy regimens including bolus and infusional application of 5-FU. The high tumor control rate of 64% and the 1-year survival rate support the approach of a sequential application of drugs effective in patients with colorectal cancer; however, future prospective trial designs have to consider issues like second- and third-line therapy on an intent-to-treat analysis to exclude a selection bias. The recent developments in combination and sequential chemotherapy in metastatic colorectal carcinoma, and the implications for the optimal treatment sequence in these patients, are still ongoing. More attention has to be paid to terms of toxicity and a more accurate reflection of the general population in clinical trials.

References

1 Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22**:229–237.

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

3 Wiseman LR, Markham A. Irinotecan. A review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer. *Drugs* 1996; 52:606–623.

4 Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; **343**:905–914.

5 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355**:1041–1047.

6 Kohne CH, Van Cutsem E, Wils J, Bokemeyer C, El-Serafi M, Lutz M, *et al.* Irinotecan improves the activity of the AIO regimen in metastatic colorectal cancer: results of EORTC GI Group study 40986. *Proc Am Soc Clin Oncol* 2003; **22**:254 (abstr 1018).

7 Becouarn Y, Gamelin E, Coudert B, Negrier S, Pierga JY, Raoul JL, *et al.* Randomized multicenter phase II study comparing a combination of fluorouracil and folinic acid and alternating irinotecan and oxaliplatin with oxaliplatin and irinotecan in fluorouracil-pretreated metastatic colorectal cancer patients. *J Clin Oncol* 2001; **19**:4195–4201.

8 Brienza S, Bensmaine MA, Soulie P, Louvet C, Gamelin E, Francois E, *et al.* Oxaliplatin added to 5-fluorouracil-based therapy (5-FU ± FA) in the treatment of 5-FU-pretreated patients with advanced colorectal carcinoma (ACRC): results from the European compassionate-use program. *Ann Oncol* 1999; **10**:1311–1316.

9 de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, *et al.* Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; **18**:2938-47.

10 WHO. *International Classification of Diseases,* 10th edn (ICD-10). Geneva: WHO; 1996.

11 Fleming TR. One-sample multiple testing procedure for phase II clinical trials. *Biometrics* 1982; **38**:143–151.

12 Kaplan EL, Maier P. Non-parametric estimation from incomplete observations. *J Am Stat Ass* 1958; **53**:457–481.

13 Hartmann JT, Kohne CH, Schmoll HJ, Daikeler T, Kanz L, Bokemeyer C. Is continuous 24-hour infusion of 5-fluorouracil plus high-dose folinic acid effective in patients with progressive or recurrent colorectal cancer? A phase II study. *Oncology* 1998; **55**:320–35.

14 Jäger E, Klein O, Wächter B, Müller B, Braun U, Knuth A. High dose 5-fluorouracil (5-FU) and folinic acid in advanced colorectal cancer resistant to standard dose 5-FU treatment: results of a phase II study [Letter]. *Eur J Cancer* 1995; **31A**:1717.

15 Hartmann JT, Harstrick A, Daikeler T, Kollmannsberger C, Muller C, Seeber S, *et al.* Phase II study of continuous 120 h infusion of mitomycin C as salvage chemotherapy in patients with progressive or rapidly recurrent colorectal cancer. *Anticancer Drugs* 1998; **9**: 427–431.

16 Ross P, Norman A, Cunningham D, Webb A, Iveson T, Padhani A, *et al.* A prospective randomized trial of protracted venous infusion 5- fluorouracil with or without mitomycin C in advanced colorectal cancer. *Ann Oncol* 1997; **8**:995–1001.

17 Van Cutsem E, Cunningham D, Bokkel Huinink WW, Punt CJ, Alexopoulos CG, Dirix L, *et al.* Clinical activity and benefit of irinotecan (CPT-11) in patients with colorectal cancer truly resistant to 5-fluorouracil (5-FU). *Eur J Cancer* 1999; **35**:54–59.

18 Rothenberg ML, Cox JV, DeVore RF, Hainsworth JD, Pazdur R, Rivkin SE, *et al.* A multicenter, phase II trial of weekly irinotecan (CPT-11) in patients with previously treated colorectal carcinoma. *Cancer* 1999; **85**:786–795.

19 Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, *et al.* Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998; **352**:1407–1412.

20 Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, *et al.* A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; **22**:23–30.

21 Grothey A, Deschler B, Kroening H, Ridwelski K, Reichardt P, Kretzschmar A *et al.* Phase III study of bolus 5-fluorouracil (5-FU)/ folinic acid (FA) (Mayo) vs weekly high-dose 24h 5-FU infusion/ FA + oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). *Proc Am Soc Clin Oncol* 2002; **21**:129a (abstr 512).