A phase II trial of modified FOLFOX as first-line chemotherapy in advanced colorectal cancer

Jian Ping Xiong*, Ling Zhang*, Lu Xing Zhong, Feng Qiu, Jun Xu, Qing Song Tao, Xiao Jun Xiang, Feng Yu and Xiao Mei Tang

The objective was to evaluate the efficacy and toxicity of leucovorin plus 5-fluorouracil combined with oxaliplatin (modified FOLFOX regimen) every 2 weeks on previously untreated advanced colorectal cancer patients in the Chinese population. Fifty-one inpatients were enrolled to receive 85 mg/m^2 oxaliplatin intravenously over a 2-h period on day 1, together with 400 mg/m^2 leucovorin over 2-h, followed by a 46-h infusion of 5-fluorouracil at 2600 mg/m^2 every 2 weeks. Treatment was given until progression or unmanageable toxicity ensued. In all, 51 patients received three or more oxaliplatin doses and a median of nine treatment cycles (range 3–16 cycles). Of the 51 eligible patients, two complete responses and 22 partial responses were observed for an overall response rate of 47.0% (95% confidence interval 35–64%). Median progression-free survival was 7.7 months (95% confidence interval 6.8–8.6) and median overall survival was 15.0 months (95% confidence interval 13.1–16.9). Toxicities were mild: five patients (9.8%) reported grade 3–4 neutropenia, 33 patients (64.8%) experienced grade 1–3 neurotoxicity and only six patients (11.8%) experienced grade 3 neurotoxicity. The leucovorin plus 5-fluorouracil combined with oxaliplatin (modified FOLFOX) regimen is active and well tolerated in patients with previously untreated advanced colorectal cancer in the Chinese population. *Anti-Cancer Drugs* 18:1103–1107 © 2007 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2007, **18:**1103–1107

Keywords: chemotherapy, colorectal cancer, leucovorin, oxaliplatin, 5-fluorouracil

Department of Oncology, The First Affiliated Hospital, Nanchang University, Nanchang, PRC

Correspondence to Dr Jian Ping Xiong, MD, Department of Oncology, The First Affiliated Hospital, Nanchang University, 17 Yongzhengwai Rd, 330006 Nanchang, PRC
Tel: +86 791 8693861; fax: +86 791 8693861;
e-mail: jpxiong@medmail.com.cn

*Jian Ping Xiong and Ling Zhang contributed equally to this work.

Received 28 January 2007 **Revised form accepted** 15 March 2007

Introduction

Colorectal cancer is the third most common cancer worldwide, with an estimated 1 023 000 new cases per year (9.4% of new cancer cases). It is the fourth most common cause of death from cancer (529 000 deaths annually) [1]. Among both men and women, incidence rates have been increasing in China. Approximately one half of all patients develop advanced disease. The prognosis for these patients is poor, although palliative chemotherapy has been shown to be able to prolong survival and to improve the quality of life with best supportive care [2]. 5-Fluorouracil (5-FU) is the backbone of treatment for colorectal cancer. Also, according to randomized trials and a meta-analysis, administration of 5-FU as a continuous infusion has been considered more efficacious compared with bolus application [3]. Furthermore, continuous infusion of 5-FU differs from bolus injection, with a more favorable toxicity profile. A lower incidence of gastrointestinal and hematologic toxicity is observed. Infusional 5-FU has been used as a weekly 24- or 48-h infusion, as well as an indefinite infusion continuing for weeks and months. Weekly or biweekly infusional regimens are gaining acceptance. In a previous trial, the monthly 5-day bolus North Central Cancer Treatment Group/Mayo Clinic regimen was compared with LV5FU2, a biweekly schedule of leucovorin (LV) and bolus-plus-infusion 5-FU, LV5FU2, proved superior in terms of response rate (RR; 32.6 vs. 14.5%), progression-free survival (PFS; 27.6 vs. 22.0 weeks) and toxicity (grade 3 or 4 in 11.1 vs. 22.9% patients), but not overall survival (OS) [4].

Oxaliplatin, a new cytotoxic agent from the diaminocyclohexane platinum family, has demonstrated activity against colon carcinoma cell lines *in vitro* and has also shown synergistic activity in experimental models [5]. Oxaliplatin clinical toxicity is also distinct from other platinum drugs: it has no renal toxicity and minimal hematotoxicity; it causes both a reversible acute, cold-related dysesthesia and a dose-limiting cumulative peripheral sensory neuropathy that usually rapidly regresses after treatment withdrawal. Several large randomized trials have confirmed the efficacy of the oxaliplatin/5-FU/LV combination as first-line therapy in advanced colorectal cancer. In a phase III trial [6], LV plus 5-FU combined with oxaliplatin (modified FOLFOX regimen) FOLFOX4 was significantly superior to the infusional regimen, LV5FU2, in RR and PFS, and the

0959-4973

combination of chronomodulated 5-FU/LV and oxaliplatin produced a significantly higher RR and superior PFS than the 5-FU/LV regimen alone [7]. In a three-arm study in 796 untreated patients with advanced colorectal cancer [8], FOLFOX4 was significantly superior to the irinotecan and bolus 5-FU/LV combination and a third regimen of oxaliplatin plus irinotecan in RR, time to progression and OS, and induced fewer grade 3 or 4 toxicities.

The current phase II trial was designed to evaluate the efficacy and safety of the modified FOLFOX regimen for Chinese patients with previously untreated advanced colorectal cancer. In this modified FOLFOX regimen, the schedule of 5-FU was altered by omitting bolus 5-FU and increasing the dose of infusional 5-FU to 2600 mg/m^2 to reduce hematologic and gastrointestinal toxicity.

Patients and methods

Eligibility

The eligibility criteria were adenocarcinoma of the colon or rectum; unresectable metastases; at least one bidimensionally measurable lesion of ≥ 2 cm; adequate bone marrow, liver and renal function; Eastern Cooperative Oncology Group performance status of 0–2; and age ≥ 18 years. Previous adjuvant chemotherapy, if given, must have been completed at least 6 months before inclusion. Patients who received earlier adjuvant treatment with oxaliplatin were not eligible. Patients with central nervous system metastases, second malignancies or disease confined to previous radiation fields were excluded. Written informed consent was required and the study was approved by the ethics committees of our center.

Chemotherapy regimen and dose modification

Modified FOLFOX consisted of 400 mg/m^2/day of LV as a 2-h infusion followed by a 46-h infusion of 2600 mg/m^2 of 5-FU, 85 mg/m^2 of oxaliplatin on day 1 only, given as a 2-h infusion in 250 ml of dextrose 5%, concurrent with LV, repeated for 2 consecutive days every 2 weeks. When LV and oxaliplatin were given concurrently via a Y-connector, both drugs were administered in 5% dextrose. Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3 receptor antagonist was used for modified FOLFOX. Disposable and electronic pumps were used in all inpatients. Treatment was continued until disease progression or unacceptable toxicity occurred or until a patient chose to discontinue treatment.

Patients were assessed before the start of each cycle using the National Cancer Institute Common Toxicity Criteria version 2.0 (NCI-CTC 2.0). Chemotherapy was delayed until recovery if absolute neutrophil count decreased to less than 1500 cells/mm^3, or platelet count decreased to less than 100 000 cells/mm^3, or if significant nonhematologic toxicity persisted. The 5-FU dose was reduced after NCI-CTC 2.0 grade ≥ 3 diarrhea, stomatitis or dermatitis occurred. Oxaliplatin was reduced for grade 3/4 neutropenia and in cases of persistent (≥ 14 days) paresthesia, or temporary (7–14 days) painful paresthesia, or functional impairment. In cases of persistent (≥ 14 days) painful paresthesia or functional impairment, oxaliplatin was omitted from the regimen until recovery.

Evaluation criteria

Physical examinations and blood counts were performed every cycle. Hepatic and renal function tests, carcinoembryonic antigen, and computed tomography scans or magnetic resonance images of measurable lesions were assessed at baseline and repeated every three cycles of treatment. Responses were assessed by at least two observers, and were confirmed by an expert independent radiologist. The Response Evaluation Criteria in Solid Tumors criteria were used to evaluate clinical response [9]. PFS was measured from the date of commencing protocol treatment to the date of first progression or death from any cause without progression. OS was measured from the date of commencing protocol treatment to the date of death from any cause. Toxicity was assessed in each treatment cycle of therapy using the NCI-CTC 2.0. Poststudy second-line chemotherapy was allowed at the discretion of the investigators and prospectively monitored for exploratory survival analysis.

Statistical considerations

The Optimal Simon two-stage phase II design was used to determine the sample size. Interim analysis was carried out when the first 15 assessable patients had been recruited [10]. If more than five responses were observed, 31 additional patients were to be recruited; otherwise, the study was to be terminated. If more than 18 responses were observed in the 46 patients, the regimen was considered sufficiently active with a significance level of 5% and power of 80% to be submitted for further evaluation. Confidence intervals (CI; 95%) for the response rates were estimated using the exact probabilities of the binomial distribution. The Kaplan–Meier method was used to calculate PFS and OS. Statistical analyses were performed using SPSS 11.0 for Windows procedures (SPSS, Chicago, Illinois, USA).

Results

Patient characteristics

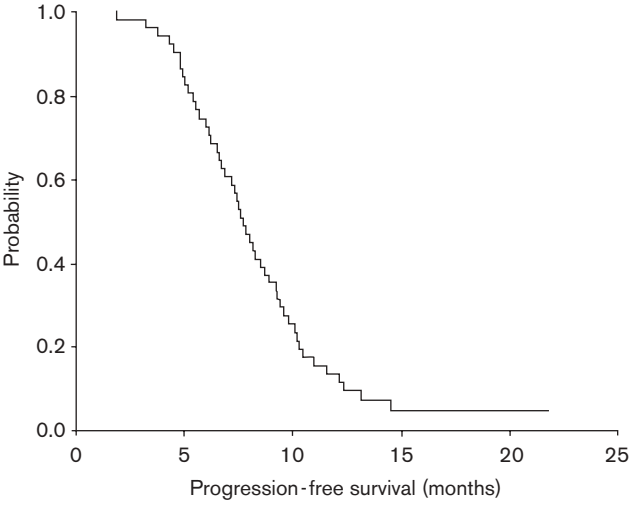
A total of 51 Chinese patients with a median age of 58.5 years (range 32–84) were registered from one center between March 2003 and September 2005. Pretreatment characteristics of these patients are listed in Table 1. In all, 51 patients received three or more doses of oxaliplatin, and were eligible to be analyzed for treatment and safety results. At the closing date of 18 September 2005, the median potential follow-up time from the commencement of treatment was 17.2 months (range 5–36 months).

Table 1 Baseline patient characteristics ($n=51$)

	No.	%
No. included	51	
Median age (years)	58.5 (32–84)	
Male/female	36/15	70.6/29.4
Primary tumor		
Colon	30	58.9
Rectum	21	41.1
Site of metastasses		
Liver	33	64.7
Lung	13	25.5
Peritoneal carcinomatosis	5	9.8
Other	16	31.4
No. of involved sites		
1	28	54.9
2 (liver and other)	11	21.6
>2	12	23.5
ECOG performance status		
0	15	29.4
1	26	51.0
2	10	19.6
CEA		
Within normal range	34	66.7
Increased	17	33.3
Prior adjuvant therapy for colorectal cancer		
No	25	48.1
Yes	26	51.9

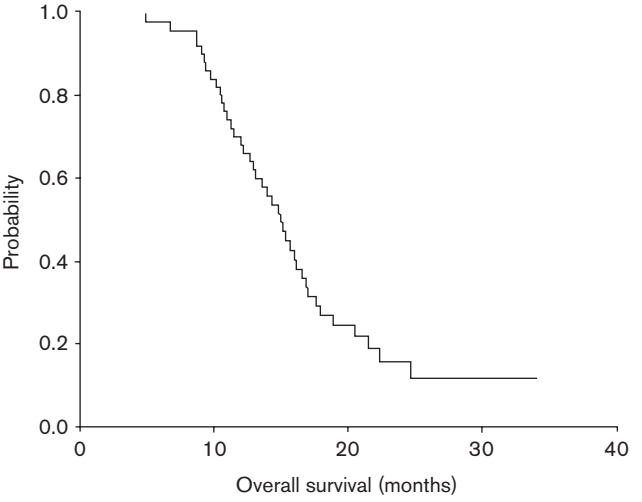
CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group.

Fig. 1



Progression-free survival for all patients.

Fig. 2



Overall survival for all patients.

Treatment given

In total, 430 cycles were given, with a range of 3–16 cycles and a median of nine cycles per patient. Out of 51 patients, 51 received three cycles or more of therapy, 47 received four cycles or more, 33 eight cycles or more and eight patients received 12 cycles or more. Although the protocol specified 14 days between cycles, 43 (10.0%) treatment cycles took place within ± 2 days of the protocol 14-day period, In total, 43 cycles (10%) were delayed for 2 days at the most and 61 cycles (14.2%) for more than 2 days. Of these, 92 cycles (21.4%) were delayed for toxicity reasons. The median relative dose intensity of oxaliplatin was 97%, of LV 100% and of infusional 5-FU 96%.

Efficacy

Of the 51 eligible patients, the best response to treatment was assessed as a complete response in two patients (3.9%) and a partial response in 22 patients (43.1%), for an overall objective RR of 47.0% (95% CI 35–64%). Fourteen (27.5%) patients had stable disease and 13 (25.5%) had progressive disease. As per the intent-to-treat analysis, the objective RR was 47.0% (95% CI 35–64%). The median PFS was 7.7 months (95% CI 6.8–8.6 months) (Fig. 1) and the median OS was 15.0 months (95% CI 13.1–16.9 months), with an estimated 68.6% of patients surviving at 1 year and 12.2% at 2 years (Fig. 2). In poststudy treatment, 17 (33.3%) patients received second-line chemotherapy (FOLFORI regimen or CapIri regimen), of whom five were still alive and 12 had died. Median OS was 20.5 months (95%CI 15.9–25.1 months). Of the 34 (66.6%) patients who did not receive second-line chemotherapy, only two patients were alive and 32 had died. Median OS was 12.1 months (95% CI 10.2–14.0 months; log-rank test $P = 0.0000$).

Toxicity

At the study closing date, of the 51 patients who had received at least three treatment cycles, eight patients (15.7%) had completed more than 12 treatment cycles and 43 patients (84.3%) had discontinued treatment. In all, 13 patients (25.6%) discontinued because of disease progression or death, 16 (31.4%) because of toxicity: nine (17.6%) neurotoxicity, five (9.8%) hematological toxicity,

Table 2 Hematological and nonhematological toxicities according to NCI-CTC ($n=51$)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Leukocytopenia	15 (29.4)	12 (23.5)	6 (11.7)	0
Neutropenia	12 (23.5)	9 (17.6%)	5 (9.8)	0
Febrile neutropenia	2 (3.9%)	0	0	0
Anemia	18 (35.2)	8 (15.7)	0	0
Thrombocytopenia	9 (17.6)	6 (11.8)	1 (1.9)	0
Nausea	24 (47.1)	7 (13.7)	4 (7.8)	0
Vomiting	17 (33.3)	5 (9.8)	3 (5.9)	0
Diarrhea	9 (17.6)	4 (7.8)	2 (3.9)	0
Constipation	8 (15.7)	3 (5.9)	0	0
Increased AST	8 (15.7)	2 (3.9)	0	0
Increased creatinine	0	0	0	0
Alopecia	6 (11.8)	1 (1.9)	NA	NA
Neurological toxicity	14 (27.5)	13 (25.5)	6 (11.8)	0
Mucositis	9 (17.6)	4 (7.8)	1 (1.9)	0
Fatigue	21 (41.2)	15 (29.4)	5 (9.8)	0

AST, aspartate aminotransferase; NA, not applicable; NCI-CTC, National Cancer Institute Common Toxicity Criteria.

and two (3.9%) other toxicity. Ten (19.6%) patients discontinued as a result of their own decisions and four (7.8%) for other reasons. Grades 1–4 acute toxicities are listed in Table 2. The most commonly reported toxicity was neutropenia. Grade 3/4 neutropenia occurred in five (9.8%) patients. There were no toxic deaths. Neurological toxicity was also common, with 14 patients (27.5%) experiencing grade 1, 13 patients (25.5%) grade 2 and six patients (11.8%) grade 3 neurotoxicity during or after treatment. No grade 4 neurotoxicity was observed. There were no toxic deaths.

Discussion

This study assessed the clinical efficacy and safety of oxaliplatin administered in combination with biweekly infusional 5-FU for patients with previously untreated advanced colorectal cancer in the Chinese population at a single center. In China, the monthly 5-day bolus Mayo Clinic regimen is a common practice in combination with oxaliplatin and 5-FU/LV. A few studies have been published in China regarding use of infusional 5-FU/oxaliplatin combination (FOLFOX) as first-line therapy for advanced colorectal cancer. Most clinical studies have used oxaliplatin in combination with LV and 5-FU. Consistent with laboratory evidence of oxaliplatin/5-FU synergy, there is evidence for the clinical activity of 5-FU/LV/oxaliplatin combinations, with RRs of 20% to more than 50% reported for the three-drug combination in phase II trials [11–13]. The combination of oxaliplatin and LV5FU2 has proven to be a major breakthrough in the treatment of colorectal cancer both in the advanced [7] and now adjuvant setting [14]. In this study, a modified FOLFOX regimen was used to treat patients with previously untreated advanced colorectal cancer. The combination regimen demonstrated promising efficacy with an RR of 47.0%, a median PFS of 7.7 months and a median OS of 15.0 months. These results were slightly lower than those reported in randomized trials of FOLFOX4 as front-line therapy and those of FOLFOX6 [15] in previously untreated advanced colorectal cancer. The main reason for this may have been fewer treatment cycles in early recruitment. This, however, is the first report of the modified FOLFOX regimen in untreated patients in China and it has confirmed that modified FOLFOX is effective in the Chinese population in the advanced setting. In addition, there was no major increase in neurotoxicity or hematological toxicity.

5-FU is one of the major cytotoxic agents for the treatment of metastatic colorectal cancer [16]. The major side effects associated with 5-FU depend on the method of administration. When the drug is given according to a 'loading' schedule of bolus treatments on five consecutive days every 4–5 weeks, neutropenia and stomatitis are the most common toxic effects. In contrast, with weekly bolus doses, diarrhea is more frequent. Regimens involving 5-FU administered as a continuous intravenous infusion (with a portable infusion pump) are associated with less hematologic and gastrointestinal toxicity, but palmar–plantar erythrodysesthesia ('hand–foot syndrome') is more common. Several studies have compared investigational regimens against the bolus-based 5-FU/LV regimens such as Mayo Clinic regimen [4,17,18]. In each case, the median OS was not significantly different from that in the control arm. The trial reported by de Gramont, *et al.* [4], however, clearly showed that the infusion-based 5-FU/LV regimen is better tolerated than the bolus-based program developed at the Mayo Clinic because there is a substantially lower frequency of diarrhea and neutropenia. In this study, the bolus 5-FU was omitted and the dose of infusional 5-FU was increased to 2600 mg/m^2, and the most commonly reported toxicity was neutropenia. Grade 3–4 neutropenia occurred in five (9.8%) patients. Grade 3–4 nausea and vomiting occurred in four (7.8) and three (5.9) patients, respectively, which occurred less frequently when compared with bolus-plus-infusion 5-FU and oxaliplatin combination [6–8,12,15,19,20]. Particularly, in two large randomized trials, when patients were assigned to receive FOLFOX4 [6] and FOLFOX6 [15] both with bolus and infusion 5-FU, neutropenia grade 3/4 occurred in 41.7 and 44% of patients respectively. In contrast, in the recent OPTIMOX2 study [21], patients were randomized to receive six cycles of modified FOLFOX7 (400 mg/m^2 of LV and 100 mg/m^2 of oxaliplatin on day 1, followed by 3000 mg/m^2 of 5-FU as a 46-h continuous infusion) with or without 5-FU/LV maintenance, and neutropenia grade 3/4 occurred in 17.2 and 11.9% of patients, respectively, during the first six modified FOLFOX7 cycles. The lowered rate of neutropenia grade 3/4 should mainly be attributed to infusional intake of 5-FU though the dose increased.

Oxaliplatin-induced neurotoxicity consists of an acute rapid-onset sensory neuropathy, often triggered by cold or sudden temperature changes, and a chronic cumulative

sensory neuropathy that occurs after several cycles of treatment, and is potentially dose limiting. In phase III study [6], 18% of patients experienced grade 3 sensory neurotoxicity; however, 74% of patients experienced a reversal of neurotoxicity after treatment was discontinued. In the randomized FOLFOX6 study, 34% had grade 3 toxicity. Similarly, in the MOSAIC study [14], grade 3 neurotoxicity was observed in 12% of patients, with 94% of patients experiencing a partial or total recovery within 6 months of stopping treatment. In this study, neurological toxicity was also common, with 33 patients (64.7%) experiencing grade 1–3 neurotoxicity, 13 patients (25.5%) experiencing grade 2 and six patients (11.8%) experiencing grade 3 during or after treatment. No grade 4 neurotoxicity was reported. 5-FU/LV, irinotecan and oxaliplatin administered alone or in combination have proven effective in the treatment of advanced colorectal cancer. Combination protocols using 5-FU/LV with either irinotecan or oxaliplatin are currently regarded as standard first-line therapies in this disease. Grothey *et al.* [22] analyzed data from seven recently published phase III trials in advanced colorectal cancer and concluded that the reported median OS is significantly correlated with the percentage of patients who received all three drugs in the course of their disease ($P = 0.0008$), but not with the percentage of patients who received any second-line therapy ($P = 0.19$). In this study, 17 (33.3%) patients received second-line chemotherapy with longer median OS (20.5 vs. 12.1 months). Unfortunately, the majority of patients did not receive second-line chemotherapy mainly because of their financial limitations.

In conclusion, the results of the present report confirm the activity of first-line modified FOLFOX in patients with advanced colorectal cancer in the Chinese population. The modified FOLFOX has good safety profiles. It should be used as a standard first-line therapy for patients with advanced colorectal cancer in China and also be studied further for benefits when combined with targeted agents (e.g. cetuximab, bevacizumab) in future studies.

References

1 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**:74–108.

2 Glimelius B, Hoffman K, Graf W, Pahlman L, Sjoden PO. Quality of life during chemotherapy in patients with symptomatic advanced colorectal cancer. The Nordic Gastrointestinal Tumor Adjuvant Therapy Group. *Cancer* 1994; **73**:556–562.

3 Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998; **16**:301–308.

4 De Gramont A, Bosset JF, Milan C, Rougier P, Bouche O, Etienne PL, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997; **15**:808–815.

5 Raymond E, Buquet-Fagot C, Djelloul S, Mester J, Cvitkovic E, Allain P, *et al.* Antitumor activity of oxaliplatin in combination with 5-fluorouracil and the thymidylate synthase inhibitor AG337 in human colon, breast and ovarian cancers. *Anticancer Drugs* 1997; **8**:876–885.

6 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**:2938–2947.

7 Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, *et al.* Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; **18**:136–147.

8 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.

9 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment in solid tumours. *J Natl Cancer Inst* 2000; **92**:205–216.

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

11 Levi FA, Zidani R, Vannetzel JM, Perpoint B, Focan C, Faggiuolo R, *et al.* Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. *J Natl Cancer Inst* 1994; **86**:1608–1617.

12 De Gramont A, Vignoud J, Tournigand C, Louvet C, Andre T, Varette C, *et al.* Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. *Eur J Cancer* 1997; **33**:214–219.

13 Andre T, Louvet C, Raymond E, Tournigand C, de Gramont A. Bimonthly high-dose leucovorin, 5-fluorouracil infusion and oxaliplatin (FOLFOX3) for metastatic colorectal cancer resistant to the same leucovorin and 5-fluorouracil regimen. *Ann Oncol* 1998; **9**:1251–1253.

14 Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, *et al.* Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; **350**:2343–2351.

15 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.

16 Kohne CH, Kretzschmar A, Wils J. First-line chemotherapy for colorectal carcinoma: we are making progress. *Onkologie* 1998; **21**:280–289.

17 Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program study. *J Clin Oncol* 1989; **7**:425–432.

18 Weh HJ, Wilke HJ, Dierlamm J, Klaassen U, Siegmund R, Illiger HJ, *et al.* Weekly therapy with folinic acid (FA) and high-dose 5-fluorouracil (5-FU) 24-hour infusion in pretreated patients with metastatic colorectal carcinoma: a multicenter study by the Association of Medical Oncology of the German Cancer Society (AIO). *Ann Oncol* 1994; **5**:233–237.

19 Giacchetti S, Bjarnason G, Garufi C, Genet D, Iacobelli S, Tampellini M, *et al.* Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy Group. *J Clin Oncol* 2006; **24**:3562–3569.

20 Goldstein D, Mitchell P, Micha M, Beale P, Friedlander M, Zalcberg J, *et al.* Australian experience of a modified schedule of FOLFOX with high activity and tolerability and improved convenience in untreated metastatic colorectal cancer patients. *Br J Cancer* 2005; **92**:832–837.

21 Maindrault-Goebel F, Lledo G, Chibaudel B, Mineur L, Andre T, Bennamoun M, *et al.* GERCOR OPTIMOX 2: A large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC): a GERCOR study. *Proc Am Clin Oncol* 2006; **24**:147s (Abstr 3504).

22 Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004; **22**:1209–1214.