Jpn J Clin Oncol 2009;39(12)791–796
doi:10.1093/jjco/hyp116

Irinotecan Plus Capecitabine as a Second-line Treatment after Failure of 5-Fluorouracil and Platinum in Patients with Advanced Gastric Cancer

Qing Sun[1], Meng Hang[1], Wei Xu[1], Weidong Mao[2], Xiaosheng Hang[3], Maoquan Li[4] and Jiaxing Zhang[4]

[1]Department of Medical Oncology, Wuxi 2nd People's Hospital, Nanjing Medical University, [2]Department of Medical Oncology, Jiangyin People's Hospital, Medical School of Nantong University, [3]Department of Medical Oncology, Wuxi Cancer Hospital, Medical School of Suzhou University, Jiangsu and [4]Radiology Clinical Center, Shanghai Tenth People's Hospital of Tongji University, Shanghai, PR China

Received June 24, 2009; accepted August 10, 2009; published online October 1, 2009

Objective: This Phase II study was conducted to evaluate the effects of irinotecan plus capecitabine in patients with advanced gastric cancer (AGC) who had received a first-line therapy of 5-fluorouracil/platinum regimen.
Methods: Patients received capecitabine 1000 mg/m^2 b.i.d. on days 1–14 followed by a 7-day rest period, and irinotecan 100 mg/m^2 was administered through a 90 min intravenous infusion on days 1 and 8, based on a 3-week cycle.
Results: Forty-six (95.8%) of the 48 patients were assessable for response. Thirteen cases of partial response were confirmed, response rate of 27.1% (95% CI, 14.5–39.7%). The median follow-up period was 25.2 months. The median time to progression and overall survival for all patients were 4.1 months (95% CI, 3.4–4.8 months) and 7.6 months (95% CI, 5.1–10.1 months). Grade 3 diarrhea and hand-foot syndrome occurred in eight (17.4%) and two (4.3%) patients, respectively. The most common Grade 3/4 hematological adverse event was neutropenia in four (8.7%) patients. There were no treatment-related deaths during this study.
Conclusion: Irinotecan plus capecitabine was a relatively active and tolerable regimen as a second-line chemotherapy for AGC. Further investigation of this regimen is warranted, including the addition of new biological agents such as bevacizumab or cetuximab to improve the salvage regimen.

Key words: advanced gastric cancer – second-line chemotherapy – irinotecan – capecitabine

INTRODUCTION

Globally, gastric cancer is the second most common cause of cancer-related mortality, with over 700 000 attributable deaths reported in 2002 (1). Although there are wide geographical variations in incidence, with peak age-standardized rates reported for East Asia (Japan and China), it has been estimated that this disease caused in excess of 188 000 deaths in Europe alone in 2006 (2). Gastric cancer is often diagnosed at an advanced stage, with approximately half of all patients presenting with unresectable, locally advanced or metastatic disease.

For reprints and all correspondence: Maoquan Li, Radiology Clinical Center, Shanghai Tenth People's Hospital of Tongji University, No. 301, Yanchang Rd, Shanghai 200072, PR China. E-mail: drmaoquan.li.md@gmail.com

Numerous classical chemotherapy agents, including 5-fluorouracil (5-FU), methotrexate (MTX), mitomycin-C, doxorubicin, cisplatinum, etoposide and epirubicin, have shown clinical activity in advanced gastric cancer (AGC). Among them, 5-FU and cisplatinum have been widely used as a component of combination therapy such as in the widely used ECF regimen (epirubicin, cisplatinum and 5-FU). Therapy with ECF is associated with significant benefits in terms of response rate (RR) and survival in patients with AGC compared with FAMTX (5-FU, adriamycin and high-dose MTX) chemotherapy in randomized Phase III studies (3,4). In addition, randomized trials have shown that the combination of 5-FU and cisplatinum is associated with improved RR and time to progression (TTP) compared with FAM (5-FU, doxorubicin and mitomycin) or 5-FU

monotherapy (5). Unfortunately, nearly half of all AGC patients will not respond to cisplatinum-based first-line chemotherapy. Furthermore, most patients who achieve response to the first-line chemotherapy will ultimately experience clinical disease progression and require second-line treatment. There is a pressing need for effective salvage treatment after the failure of first-line chemotherapy in AGC.

Irinotecan (Camptor®; Pfizer) is a semisynthetic plant alkaloid camptothecin, which inhibits DNA topoisomerase-I. SN-38 has been identified to be the important metabolite of irinotecan, and to inhibit the regulation of DNA during cell replication. In recent meta-analysis of chemotherapies used to treat AGC, a comparison between irinotecan-containing versus non-irinotecan-containing combinations (mainly 5-FU/cisplatin) showed a non-survival benefit in favor of irinotecan-containing regimens (HR = 0.88) (6). Capecitabine (Xeloda®; Roche) is an oral fluoropyrimidine that selectively generates higher levels of 5-FU in cancer tissues than in normal tissues via the action of thymidine phosphorylase. Capecitabine monotherapy was proved to be active against AGC with the RR ranged from 19.4% to 34%; moreover, median survival duration in these studies was comparable to other double or triple combination chemotherapies (7,8). In addition, in preclinical xenograft models, capecitabine was highly active against both 5-FU-sensitive and -resistant tumors (9).

Irinotecan and capecitabine in combination could be possible to have a synergistic effect in previous pre-clinical and clinical studies (10–14). Irinotecan reduces DNA synthesis, increases dTTP pools and inhibits dUMP synthesis, which are also associated with the anti-tumor activity of capecitabine (11). Actually, irinotecan/capecitabine combination regimens have been used to treat several types of solid tumors (15–18). On the basis of these promising results, we conducted this Phase II study to evaluate the effects of irinotecan plus capecitabine in patients with AGC who had received a first-line therapy of 5-FU/platinum regimen.

PATIENTS AND METHODS

Eligibility Criteria

All the patients involved in the current study had histologically confirmed metastatic or recurrent gastric adenocarcinoma with at least one unidimensionally measurable lesion (i.e. a diameter $\geq$1 cm, as assessed by spiral computed tomography). The patients were 18–75 years of age with a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale. Plus, adequate hematological (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l and hemoglobin $\geq$9 g/dl), renal (serum creatinine $\leq$1.5 mg/dl and creatinine clearance $\geq$50 ml/min) and hepatic (total bilirubin $\leq$2.0 mg/dl and serum transaminase level $\leq$3 times the upper limit of the normal range) levels were also required, and prior exposure and failure to a combination of 5-FU and platinum (cisplatin, heptaplatin or oxaliplatin) chemotherapy. Exclusion criteria included: gastric or esophageal cancer other than adenocarcinoma; central nervous system metastases; unresolved bowel obstruction or sub-obstruction; chronic diarrhea; other serious medical conditions (unstable cardiac disease requiring treatment); uncontrolled angina pectoris; myocardial infarction within 6 months; active uncontrolled infections, uncontrolled diabetes with symptomatic peripheral neuropathy); any history of anaphylaxis to drugs; and history of other cancer within the past 5 years, except for curatively treated non-melanoma skin cancer or *in situ* carcinoma of the cervix. The institutional review board of author's institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Study Treatment

All the treatments were administered on an outpatient basis. Capecitabine 1000 mg/m^2 b.i.d. with pyridoxine 100 mg t.i.d. was given on days 1–14 followed by a 7-day rest period. The capecitabine was supplied as film-coated tablets at two dose strengths, 150 and 500 mg, whereas the irinotecan 100 mg/m^2 was administered through a 90 min intravenous infusion on days 1 and 8, based on a 3-week cycle. The dose schedule of this study was based on the early encouraging results from Phase I/II trials evaluating XELIRI/CAPIRI regimens (capecitabine at 1000 mg/m^2 for 2 weeks plus irinotecan at 240–250 mg/m^2 on day 1 or 80–100 mg/m^2 on days 1 and 8) (19–22). All patients received 5-HT3 inhibitors for emesis prophylaxis. Treatment continued until disease progression or intolerable toxicity. Patients who achieved a complete response (CR) could receive an additional two cycles of treatment at the investigator's discretion. Doses were recalculated before each cycle and adjusted as needed.

Dose Modification

A physical examination was carried out before each cycle of therapy. Complete blood counts and biochemical tests were performed before each cycle. Safety was evaluated before each treatment cycle according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Hand-foot syndrome (HFS) was graded as described previously (23). Patients were required to meet all of the following criteria to begin the next cycle of treatment: neutrophil count $\geq 1.5 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l and resolution or improvement of clinically significant non-hematologic adverse events to Grade 1 or 0. Patients were excluded if treatment was delayed for 2 weeks. Dosage modification could be made on day 1 of a new cycle (on the basis of laboratory values obtained on that day and the adverse events encountered during the preceding cycle). Safety assessment and dose adjustments of capecitabine for HFS were as follows: no reductions for Grade 1; a 25% reduction for Grade 2 and a 50% reduction for Grade 3 HFS.

Any patient who required more than a 50% dose reduction was withdrawn from the study.

Response to Treatment and Adverse Effects

The primary endpoint of this study was RR, and secondary endpoints were toxicity, TTP and overall survival (OS). Before entering the study, all patients received physical examination, full blood count and serum chemistry analyses. Chest X-ray, ECG, upper gastrointestinal endoscopies, abdominal computer tomographic (CT) scans and other appropriate procedures were also performed as needed. After every two cycles of treatment, response was evaluated using RECIST criteria. Of the lesions observed prior to treatment, a maximum of five measurable lesions from each metastasized organ up to a total of 10 lesions were selected as target lesions. In cases of partial response (PR) or CR, a confirmative CT scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles. Toxicity was graded according to Version 2.0 of the National Cancer Institute-Common Toxicity Criteria (NCI-CTC). Tumor-related symptoms were assessed at baseline and before each cycle.

Statistical Analysis

The current trial used a two-stage optimal design, as proposed by Simon (24), with an 80% power to accept the hypothesis and 5% significance to reject the hypothesis. According to the published data of RR of 16.3–24% from most second-line chemotherapy trials in patients with AGC refractory to fluoropyrimidine and/or platinum (25–27), the current trial was designed to detect an RR of 40% when compared with a minimal, clinically meaningful RR of 20%. Allowing for a follow-up loss rate of 10%, the total sample size was 48 patients with a measurable disease. All enrolled patients were included in the intention-to-treat analysis of efficacy. The duration of response, TTP and survival analyses were all estimated using the Kaplan–Meier method. The duration of response was defined as the interval from the onset of a CR or PR until evidence of disease progression was found. Meanwhile, the TTP was calculated from the initiation of chemotherapy to the date of disease progression, whereas OS was measured from the initiation of chemotherapy to the date of the last follow-up or death. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

From June 2005 to July 2007, a total of 48 patients were enrolled in the current study. The characteristics of the patients are summarized in Table 1. The median age was 55 (range, 24–72) years, with 35 males and 13 females. Most of the patients (87.5%) had a good performance status (ECOG 0 or 1). Distal lymph nodes, peritoneum and liver were the most common sites of the metastases. Primary gastrectomy had been performed in all patients. Nine (18.8%) patients received neoadjuvant chemotherapy, 20 (41.7%) received adjuvant chemotherapy and 10 (20.8%) received post-operative chemoradiotherapy. Initial therapy for recurrence/metastases consisted of either 5-FU plus cisplatin (79.2%) or 5-FU plus oxaliplatin (20.8%).

Table 1. Patient characteristics ($n = 48$)

Characteristics	Number of patients (%)
Age (years)	
Median (range)	55 (24–72)
Male/female	35/13
ECOG PS	
0	10 (20.8)
1	32 (66.7)
2	6 (12.5)
Location of primary tumor	
Cardia/fundus	11 (22.9)
Body/antrum	34 (70.8)
Diffuse	3 (6.3)
Histology	
Well/moderately adenocarcinoma	18 (37.5)
Poorly/undifferentiated or signet-ring cell carcinoma	30 (62.5)
Metastatic sites	
Lymph node	34 (70.8)
Liver	16 (33.3)
Peritoneum	24 (50.0)
Lung	7 (14.6)
Bone	6 (12.5)
Others (ovary, kidney, pancreas)	3 (6.3)
Number of metastases	
1	19 (39.6)
2	15 (31.3)
≥ 3	13 (27.1)
Primary therapy	
Primary gastrectomy	48 (100.0)
Neoadjuvant chemotherapy	9 (18.8)
Adjuvant chemotherapy	20 (41.7)
Post-Op chemoradiotherapy	10 (20.8)
Initial therapy for recurrence/metastases	
5-FU/cisplatin	38 (79.2)
5-FU/oxaliplatin	10 (20.8)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; Post-Op, post-operative; 5-FU, 5-fluorouracil.

Table 2. Tumor response (intention-to-treat analysis, $n = 48$)

Response	*n* (%)
Complete response	—
Partial response	13 (27.1)[a]
Stable disease	21 (43.8)
Progressive disease	12 (25.0)
Not assessable	2 (4.2)

[a]95% confidential interval = 14.5 – 39.7%.

Efficacy and Survival

Forty-six (95.8%) of the 48 patients were assessable for response; of the two patients not assessable, both were lost to follow-up after the second cycle of the treatment. All efficacy data are reported using the intent-to-treat patient population. Thirteen cases of PR were confirmed, RR of 27.1% (95% CI, 14.5–39.7%). Of 13 responses, 1 (7.7%) were observed after two cycles, 3 (23.1%) after three cycles, 7 (53.8%) after four cycles and 2 (15.4%) after six cycles (Table 2). The median follow-up period was 25.2 months. The median TTP for all patients was 4.1 months (95% CI, 3.4–4.8 months). The estimated median OS was 7.6 months (95% CI, 5.1–10.1 months) (Fig. 1). The estimate of OS at 12 months was 25.8% (95% CI, 12.5–39.1%). The median duration of response was 2.5 months (95% CI, 1.4–3.3 months).

Toxicity

Forty-six (95.8%) patients were assessable for safety. Toxic effects observed during the study are listed in Table 3. Most patients experienced neutropenia during their course of therapy with 6.5% of patients ($n = 3$) for Grade 3 and 2.2% ($n = 1$) for Grade 4 neutropenia. Grade 1 or 2 neutropenia was detected in 56.5% of patients ($n = 26$). Grade 3 febrile neutropenia were documented in two (4.3%) patients. Nausea, vomiting, diarrhea and HFS were the most common non-hematological toxicities. Grade 3 nausea, vomiting, diarrhea and HFS were observed in one (2.2%), two (4.3%), eight (17.4%) and two (4.3%) patients, respectively. However, no Grade 4 non-hematologic toxicity was observed in this study. Grade 1 or 2 nausea, diarrhea and HFS were detected in 34 (73.9%), 21 (45.7%) and 25 (54.3%) patients, respectively. No patients were discontinued from the study due to toxic effects. There were no treatment-related deaths during this study.

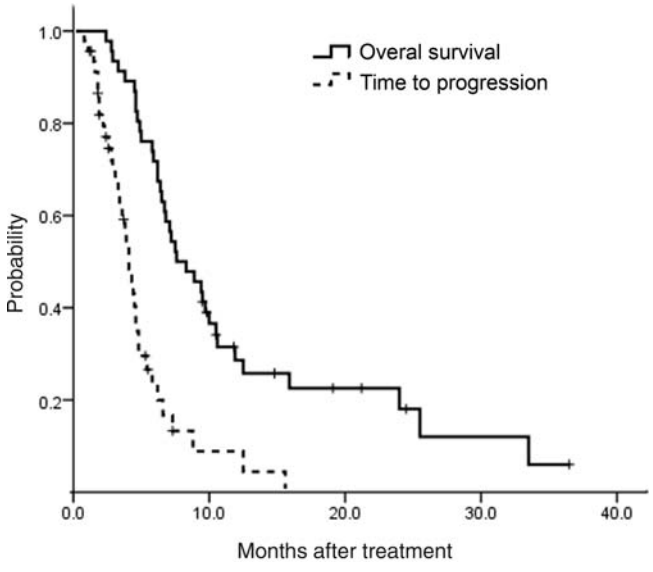

Figure 1. Time to disease progression and overall survival for all patients.

Table 3. Toxicities of irinotecan plus capecitabine combination chemotherapy for patients with advanced gastric cancer (by patients)

	Grade (*n*, % of patients, $n = 46$)[a]			
	1	2	3	4
Hematologic				
Anemia	16 (34.8)	13 (28.3)	0	0
Neutropenia	9 (19.6)	17 (37.0)	3 (6.5)	1 (2.2)
Febrile neutropenia	14 (30.4)	8 (17.4)	2 (4.3)	0
Thrombocytopenia	2 (4.3)	0	0	0
Non-hematologic				
Nausea	26 (56.5)	8 (17.4)	1 (2.2)	0
Vomiting	8 (17.4)	10 (21.7)	2 (4.3)	0
Stomatitis	7 (15.2)	8 (17.4)	0	0
Alopecia	11 (23.9)	6 (13.0)	0	0
Diarrhea	13 (28.3)	9 (19.6)	8 (17.4)	0
Hand-foot syndrome	21 (45.7)	4 (8.7)	2 (4.3)	—

[a]National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0, except for grading of hand-foot syndrome.

DISCUSSION

Unresectable advanced or metastatic gastric cancer still has a poor prognosis, with a median survival of just 7–10 months. Several combinations regimens of chemotherapy have been developed, but the survival advantage appears to be marginal, and no worldwide standard regimens have as yet been established. Recent meta-analysis has been carried out to assess the efficacy and tolerability of chemotherapy in patients with AGC. Analysis of chemotherapy versus best supportive care (HR = 0.39, 95% CI 0.28–0.52) and combination versus single agent, mainly 5-FU (HR = 0.83, 95% CI 0.74–0.93), demonstrated significant OS results in favor of chemotherapy and combination chemotherapy (6). However, most patients receiving first-line chemotherapy

eventually develop progressive disease, whereas there is no established second-line regimen.

In this study, we found that irinotecan plus capecitabine was an active and safe salvage chemotherapy when used in routine clinical practice for patients with AGC for whom 5-FU and platinum-based first-line chemotherapy had previously failed. This study demonstrated that capecitabine 1000 mg/m^2 b.i.d. on days 1–14 followed by a 7-day rest period, and irinotecan 100 mg/m^2 was administered through a 90 min intravenous infusion on days 1 and 8, based on a 3-week cycle, was active and well tolerated as a second-line therapy in pretreated patients with AGC. The overall RR was 27.1%, and median TTP and OS were 4.1 and 7.6 months, respectively. In the current study, the efficacy was comparable to the published data from most second-line chemotherapy for patients with AGC refractory to fluoropyrimidine and/or platinum. Taguchi (25), Vanhoefer (26) and Lee et al. (27), respectively, reported a 24% RR with docetaxel 60 mg/m^2 in 59 patients, a 20% RR with docetaxel 100 mg/m^2 in 25 patients and a 16.3% RR with docetaxel 75 mg/m^2 in 49 patients who had already been exposed to first-line 5-FU and cisplatin, respectively.

In the current study, overall, the treatment was well tolerated. A Phase II study by Kim et al. (28) reported that a capecitabine plus cisplatin regimen produced a high RR of 54.8% and median OS of 10.1 months in patients with AGC. In contrast, the current study used a reduced dose of capecitabine, 1000 mg/m^2 instead of 1250 mg/m^2, owing to the relatively high incidence of HFS. Grade 2/3 HFS has previously been observed in 27.5–50% of patients with AGC who received the standard dose of capecitabine (28,29), and as there is no effective prophylaxis or treatment for HFS, this can interrupt treatment or reduce the dose intensity of capecitabine. In the current study, only six patients (13.0%) experienced Grade 2/3 HFS.

The major toxicities related to irinotecan are diarrhea and myelosuppression, which are known to be dose dependent. Chemotherapy-induced severe diarrhea or neutropenia can also result in treatment-related hospitalization or mortality, thereby compromising the quality of life and increasing medical expenditure. In a randomized multicenter Phase II trial comparing two different schedules of irinotecan combined with capecitabine as the first-line treatment for metastatic colorectal cancer (30), diarrhea, which occurred in 37.8% of the patients at a Grade 3/4 intensity, was the main adverse effect of the arm B regimen (capecitabine 1000 mg/m^2 twice daily on days 2–15 and irinotecan 120 mg/m^2 on days 1 and 8, every 21 days). However, in the present study, a reduced dose of irinotecan (100 mg/m^2 on days 1 and 8) was administered to alleviate adverse effects, and Grade 3/4 diarrhea and neutropenia were only observed in 17.4% and 6.5% of the patients, respectively, which are consistent with previous findings (18). No patients were discontinued from the study due to toxic effects. Furthermore, there was no treatment-related death or Grade 4 nonhematological adverse events in the current study.

In conclusion, irinotecan plus capecitabine was a relatively active and tolerable regimen as a second-line chemotherapy for AGC. Further investigation of this regimen is warranted, including the addition of new biological agents such as bevacizumab or cetuximab to improve the salvage regimen.

Acknowledgements

The authors are grateful to all the staff at the study centers who contributed to this study.

Conflict of interest statement

None declared.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
2. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;18:581–92.
3. Waters JS, Norman A, Cunningham D, Scarffe JH, Webb A, Harper P, et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. *Br J Cancer* 1999;80:269–72.
4. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;15:261–7.
5. Kim NK, Park YS, Heo DS, Suh C, Kim SY, Park KC, et al. A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. *Cancer* 1993;71:3813–8.
6. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and metaanalysis based on aggregate data. *J Clin Oncol* 2006;24:2903–9.
7. Koizumi W, Saigenji K, Ujiie S, Terashima M, Sakata Y, Taguchi T. A pilot phase II study of capecitabine in advanced or recurrent gastric cancer. *Oncology* 2003;64:232–6.
8. Hong YS, Song SY, Lee SI, Chung HC, Choi SH, Noh SH, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. *Ann Oncol* 2004;15:1344–7.
9. Cao S, Lu K, Ishitsuka H, Rustum YM. Antitumor efficacy of capecitabine against fluorouracil-sensitive and -resistant tumours. *Proc Am Soc Clin Oncol* 1997;16:226 (abstr 795).
10. Guichard S, Hennebelle I, Bugat R, Canal P. Cellular interactions of 5-fluorouracil and the camptothecin analogue CPT-11 (irinotecan) in a human colorectal carcinoma cell line. *Biochem Pharmacol* 1998;55:667–76.
11. Mullany S, Svingen PA, Kaufmann SH, Erlichman C. Effect of adding the topoisomerase I poison 7-ethyl-10-hydroxycamptothecin (SN-38) to 5-fluorouracil and folinic acid in HCT-8 cells: elevated dTTP pools and enhanced cytotoxicity. *Cancer Chemother Pharmacol* 1998;42:391–9.
12. Azrak RG, Cao S, Slocum HK, Toth K, Durrani FA, Yin MB, et al. Therapeutic synergy between irinotecan and 5-fluorouracil against human tumor xenografts. *Clin Cancer Res* 2004;10:1121–9.
13. Cao S, Durrani FA, Rustum YM. Synergistic antitumor activity of capecitabine in combination with irinotecan. *Clin Colorectal Cancer* 2005;4:336–43.
14. Rea DW, Nortier JW, Ten Bokkel Huinink WW, Falk S, Richel DJ, Maughan T, et al. A phase I/II and pharmacokinetic study of irinotecan in combination with capecitabine as first-line therapy for advanced colorectal cancer. *Ann Oncol* 2005;16:1123–32.

15. Borner MM, Bernhard J, Dietrich D, Popescu R, Wernli M, Saletti P, et al. A randomized phase II trial of capecitabine and two different schedules of irinotecan in first-line treatment of metastatic colorectal cancer: efficacy, quality-of-life and toxicity. *Ann Oncol* 2005;16:282–8.
16. Han JY, Lee DH, Lee SY, Park CG, Kim HY, Lee HG, et al. Phase II study of weekly irinotecan plus capecitabine for chemotherapy-naive patients with advanced nonsmall cell lung carcinoma. *Cancer* 2005;104:2759–65.
17. Kim TW, Kang WK, Chang HM, Park JO, Ryoo BY, Ahn JS, et al. Multicenter phase II study of oral capecitabine plus irinotecan as first-line chemotherapy in advanced colorectal cancer: a Korean Cancer Study Group trial. *Acta Oncol* 2005;44:230–5.
18. Baek JH, Kim JG, Jeon SB, Chae YS, Kim DH, Sohn SK, et al. Phase II study of capecitabine and irinotecan combination chemotherapy in patients with advanced gastric cancer. *Br J Cancer* 2006;94:1407–11.
19. Kerr DJ, Ten Bokkel Huinink WW, Ferry DR, Rea DW, Boussard BM, Oulid-Aissa D, et al. A phase I/II study of CPT-11 in combination with capecitabine as first line chemotherapy for metastatic colorectal cancer (MCRC). *Proc Am Soc Clin Oncol* 2002;21 (abstr 643).
20. Tewes M, Schleucher N, Achterrath W, Wilke HJ, Frings S, Seeber S, et al. Capecitabine and irinotecan as first-line chemotherapy in patients with metastatic colorectal cancer: results of an extended phase I study. *Ann Oncol* 2003;14:1442–8.
21. Jordan K, Grothey A, Kellner A, Constantin C, Dietrich G, Schlichting C, et al. Randomized Phase II trial of capecitabine plus irinotecan versus capecitabine plus oxaliplatin as first-line therapy in advanced colorectal cancer (ACRC): results of an interim analysis. *Proc Am Soc Clin Oncol* 2002;21 (abstr 103b).
22. Cassata A, Stani SC, Alu M, Procopio G, Cortinovis D, Beretta E, et al. Ongoing Phase II trial with two schedules of irinotecan (CPT-11) in combination with capecitabine as first line chemotherapy in patients with advanced colorectal cancer (ACRC). *Proc Am Soc Clin Oncol* 2001;20 (abstr 144a).
23. Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999;17:485–93.
24. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
25. Taguchi T. A late phase II study of docetaxel in patients with gastric cancer. *Proc Am Soc Clin Oncol* 1997;15 (abstr 934).
26. Vanhoefer U. Phase II study of docetaxel as second-line chemotherapy in metastatic gastric cancer. *Proc Am Soc Clin Oncol* 1999;18 (abstr 1163).
27. Lee JL, Ryu MH, Chang HM, Kim TW, Yook JH, Oh ST, et al. A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy. *Cancer Chemother Pharmacol* 2008;61:631–7.
28. Kim TW, Kang YK, Ahn JH, Chang HM, Yook JH, Oh ST, et al. Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced gastric cancer. *Ann Oncol* 2002;13:1893–8.
29. Park YH, Ryoo BY, Choi SJ, Kim HT. A phase II study of capecitabine and docetaxel combination chemotherapy in patients with advanced gastric cancer. *Br J Cancer* 2004;90:1329–33.
30. Bajetta E, Di Bartolomeo M, Mariani L, Cassata A, Artale S, Frustaci S, et al. Randomized multicenter Phase II trial of two different schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. *Cancer* 2004;100:279–87.