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CLINICAL TRIAL REPORT

A phase II study of combination therapy with irinotecan and S-1 (IRIS) in patients with advanced colorectal cancer

Manabu Shiozawa · Makoto Akaike · Nobuhiro Sugano · Kazuhito Tsuchida · Naoto Yamamoto · Soichiro Morinaga

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Abstract
Purpose A combination of irinotecan with continuous infusional 5-fluorouracil (5-FU) is the standard treatment for advanced colorectal cancer. The aim of this study was to determine the efficacy and safety of combining irinotecan and S-1 (IRIS) in patients with advanced colorectal cancer.
Methods Irinotecan was administered as an intravenous infusion at a dose of 120 mg/m^2 on day 1 and 15. And S-1 was administered orally on days 1–14 of a 28-day cycle. S-1 was given orally at a dose that did not exceed 40 mg/m^2 based BSA: BSA < 1.25 m^2, 40 mg twice daily; 1.25–1.5 m^2, 50 mg twice daily, and BSA > 1.5 m^2, 60 mg twice daily, for 14 consecutive days.
Results A total of 38 patients were enrolled. An intent-to-treat analysis showed a complete response and partial response to occur in 13.2% and 50.0%, respectively. The disease control rate was 84.2%. The median progression-free survival and overall survival were 10.0 months and 29.1 months, respectively. The rates of grade 3/4 toxicity over 4 cycles were the following: neutropenia, 15.8%; leucopenia, 7.9%; anorexia, 15.8%; diarrhea, 10.5%. Conclusion: IRIS is an effective, well tolerated and convenient treatment regimen for patients with advanced colorectal cancer.

Keywords S-1 · Irinotecan · IRIS · Advanced colorectal cancer

M. Shiozawa (✉) · M. Akaike · N. Sugano · K. Tsuchida · N. Yamamoto · S. Morinaga
Department of Gastrointestinal Sugery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan
e-mail: shioz@coral.ocn.ne.jp

Introduction

5-fluorouracil (5-FU) is the key drug for the treatment of advanced colorectal cancer. It is used with other drugs, such as leucovorin and irinotecan, to increase effectiveness of anticancer drugs. A recent study shows the excessive toxicity when bolus 5-FU, leucovorin, and irinotecan are combined [1, 2]. An infusional 5-FU regimens offer efficacy and safety benefits over bolus intravenous administration [3, 4]. A combination of irinotecan and continuous intravenous infusional 5-FU and leucovorin as the first-line treatment provides a survival benefit in patients with advanced colorectal cancer [5–9]. However, the administration of infusional 5-FU is associated with more complications, discomfort, and inconvenience because of the need for central venous access and portable infusion pumps [10, 11]. Therefore, new oral fluoropyrimidine agents, such as S-1, UFT (uracil/tegafur), and Capecitabine, are administered instead of infusional 5-FU to avoid such complications.

S-1 is an oral fluoropyrimidine preparation. It is an anticancer that might replace 5-FU. It is a novel oral fluorouracil antitumor drug that contains a combination of 3 pharmacological agents : tegafur (FT), a 5-fluorouracil (5-FU) prodrug, 5-chloro-2,4-dihydroxypyridine (CDHP), which inhibits the activity of dihydropyrimidine dehydrogenase (DPD), and potassium oxonate (Oxo), which reduces the gastrointestinal toxicity of 5-FU [12]. The convenient oral route of administration, antitumor activity, and improved toxicity profile in comparison to intravenous 5-FU together makes S-1 an attractive option for combining it with intravenous irinotecan in the treatment of advanced colorectal cancer [13].

This current study was designed to be a phase II trial to evaluate the safety and clinical efficacy of combining S-1

orally and irinotecan in patients with advanced or metastatic colorectal cancer. Bi-weekly irinotecan schedules were selected based on the results of the phase I trial [14]. S-1 was administered for 2 weeks on with 2-weeks rest period, and then both irinotecan and S-1 were thereafter repeated every 4 weeks.

Patients and methods

Patient eligibility

This was a non-randomized, open-label, phase II study, performed at Kanagawa Cancer Center, Yokohama, Japan. All patients entered in this study had histologically confirmed advanced or metastatic colorectal cancer. Eligibility criteria included age 20–75, estimated life expectancy of more than 16 weeks, Eastern Cooperative Oncology Group (ECOG) performance status 0, and adequate hematological (absolute white blood cell count >3,000/mm^3, neutrophil count > 1,500/mm^3, platelets >100,000/mm^3, Hb >10 g/dl), hepatic (AST and ALT within 2 times the upper limit of normal for the institution, serum bilirubin level below 1.5 mg/dl) and renal (serum creatinine level below 1.5 mg/dl and BUN under 25 mg/dl) function, with at least one measurable site of disease (>1 cm in at least one dimension). No patients accepted into this had received any prior chemotherapy, except for adjuvant chemotherapy completed more than 6 months before study entry. Written informed consent was obtained from all patients and the protocol was approved by the institutional ethics committee. Patients were excluded from this trial for any of the following exclusion criteria: symptomatic infectious disease, bleeding tendency, severe heart disease, pre-existing symptomatic peripheral neuropathy, active double cancer, symptomatic ascites, pregnancy, breast feeding, obstructive bowel disease, and severe diabetes mellitus requiring insulin or past history of drug allergy.

Treatment plan

Irinotecan was administered by intravenous infusion at a dose of 120 mg/m^2 over 90 min on day 1 and 15. S-1 was administered orally on days 1–14 of a 28-day cycle, based on the results of the phase I trial [14]. The dose of S-1 was determined according to the basis of patient's body surface area (BSA). It was given orally at a dose that did not exceed 40 mg/m^2 based BSA: BSA <1.25 m^2, 40 mg twice daily; 1.25–1.5 m^2, 50 mg twice daily, and BSA >1.5 m^2, 60 mg twice daily, for 14 consecutive days. All patients were premedicated with 5-hydroxytryptamine-3-receptor antagonist combined with 10 mg of dexamethasone before administration of irinotecan. This treatment course was repeated every 4 weeks until confirmation of either disease progression or serious adverse events. Dose delays and/or modifications of irinotecan or/and S-1 were performed based on any observed toxicity. If relevant hematological or non-hematological toxicities of grade 3 or 4 according to the National Cancer Institute Common Toxicity criteria scale, version 3.0, occurred, subsequent courses of treatment were withheld until the resolution of these adverse events to the levels of eligibility criteria. A reduction of irinotecan was based on the occurrence of a grade 3 or 4 adverse events in two consecutive cycles or the occurrence of treatment delay up to 2 weeks to recover from adverse events. The dose of irinotecan was reduced in subsequent course from 120 mg/m^2 to 100 mg/m^2. If doses were withheld because of adverse events, the days that therapy was omitted were still counted as part of the 28-day treatment cycle. The dose of S-1 was unchanged if the dose of irinotecan was reduced. The dose of S-1 was reduced in the subsequent course: 60 mg, 50 mg, and 40 mg of S-1 twice daily were reduced to 50 mg, 40 mg, and 25 mg twice daily, respectively if the patients could not intake S-1 because of stomach ache, nausea, and vomiting. Once lowered, the doses of S-1 and irinotecan were not increased thereafter.

Evaluation of safety and response

Pretreatment evaluation included a medical history, physical examination, a complete blood cell count, serum biochemical profile (liver function tests, renal function tests, creatinine clearance determination), urinalysis and electrocardiogram. A chest X-ray and computed tomographic scan of the chest and abdomen were performed. All patients were reviewed weekly for symptoms of toxicity and underwent clinical examinations, including determination of weight and performance status during the study period. Blood cell count, liver and renal function tests were performed once every week. Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0. CT scanning and imaging of measurable disease were performed every 8 weeks. The tumor response was determined according to the RECIST criteria [15]. A complete response (CR) was defined as the disappearance of all evidence of cancer for more than 16 weeks. A partial response (PR) was defined as at least a 30% reduction in the sum of the products of the perpendicular diameters of all lesions for more than 16 weeks, without any evidence of new lesions or progression of the lesions. Stable disease (SD) was defined as less than a 30% reduction or less than 20% increase in the sum of the products of the perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease (PD) was defined as more than a 20% increase in more than 1 lesion,

or the appearance of new lesions. All responses were subjected to independent verification. For the patients who showed a good response to the treatment, the response duration was defined as the time from the commencement of the treatment protocol until the first documentation of either progression or relapse. Both the safety profiles and dose intensity were determined for up to 4 courses of treatment per patient.

Statistical analysis

Our previous phase I study of S-1 combined with irinotecan treatment [14] suggested a response rate of 50%. The required sample size for this study on the target activity level of 50% and a minimum activity level of 30%, with an α error of 0.05 and β error of 0.2 was estimated to be 34. The progression-free survival and overall survival were estimated using the Kaplan–Meier product-limit method from the date of starting treatment. The 95% confidential interval for the median progression-free and overall survival was estimated by the log-rank test.

Results

Patients Characteristics

Between January 2005 and April 2009, a total of 38 patients were enrolled in this phase II study. There were 21 men and 17 women, ranging in age from 36 to 75 (median age, 63). The patient's characteristics are shown in Table 1. Eleven patients had received prior adjuvant chemotherapy (bolus 5-FU and l-LV in 4, and oral fluoropyrimidine derivative in 6), and 27 patients had a surgery for the primary tumor only. All patients were PS 0. Tumor differentiation was mostly moderate (65.8%). The most common metastatic site was the liver (55.3%). The total number of chemotherapy cycles completed by the patients ranged from 1 to 40 (median 9 courses).

Treatment response

Efficacy was assessed in all of the 38 patients (ITT population). The patients who received at least two cycles of treatment were evaluable for response. Response was not evaluated in four patients (10.5%) because of toxicity before the initial evaluation of response. These patients were classified as non-responders in the ITT analysis. The overall response rate in the ITT population was 63.1% shown in Table 2 (five complete response, nineteen partial response), with eight patients having stable disease (SD) and two progressive disease after treatment. The disease control rate was 84.2%. The mean relative dose intensity during 4 courses of S-1 and irinotecan was 86.0% and 83.2%, respectively.

Table 1 Patient's characteristics

Age (years)	36–75 (Median:63)
Gender	
Male	21
Female	17
PS (ECOG):0	38
Primary lesion	
Colon	19
Rectum	19
Number of metastatic sites	
1	32
2	5
≧3	1
Prior therapy	
Adjuvant chemotherapy	11
Surgery for primary lesions	27
Differentiation	
Well	11
Moderate	25
Mucinous	1
Poor	1
Site of metastasis	
Liver	21
Lung	10
Lymph node	5
Abdominal mass	8
Others	1

At a median follow-up time of 20 months, the median progression-free survival time was 10.0 months (range, 2.0–30.0 months; 95% confidence interval, 8.0–12.0 months; Fig. 1). At the end of the study, nineteen patients died of advanced cancer and 19 patients were alive. The median overall survival time was 29.1 months (range, 5.9 to 43.2 months; 95% confidence interval, 17.8 to 40.5 months; Fig. 2).

Toxicity

Toxicity is summarized according to the worst grade per patient during four-courses in Table 3. No patients died from any adverse events. The most common type of hematological toxicity was neutropenia, which was generally mild. The common types of non-hematological toxicities were nausea, anorexia, diarrhea, and alopecia. However, there was no incidence of grade 4 non-hematological toxicity. No patients experienced grade >2 liver and renal dysfunction. Four of 38 patients (10.5%) discontinued only the first course of this regimen because of toxicities. The toxicities

Table 2 Phase II studies of combination therapy with irinotecan and S-1

Author	Regimen (weeks)	Patients	RR (%)	Dose (mg/m^2/week)	Median PFS (months)
Goto et al. [16]	CPT-11 (150 mg/m^2) days 1 + S-1(80 mg/m^2) days 1–14 q 3	40	62.5	CPT-11 50.0 S-1 373.3	8.0
Tsunoda et al. [17]	CPT-11 (80 mg/m^2) days 1,15 + S-1(80 mg/m^2) days 1–21 q 5	40	62.5	CPT-11 32.0 S-1 336.0	7.8
Yuki et al. [18]	CPT-11 (100 mg/m^2) days 1,15 + S-1(80 mg/m^2) days 1–14 q 4	40	52.5	CPT-11 50.0 S-1 280.0	8.7
Current study	CPT-11 (120 mg/m^2) days 1,15 + S-1(80 mg/m^2) days 1–14 q 4	38	63.1	CPT-11 60.0 S-1 280.0	10.0

PFS progression-free survival, *CPT* irinotecan, *RR* response rate

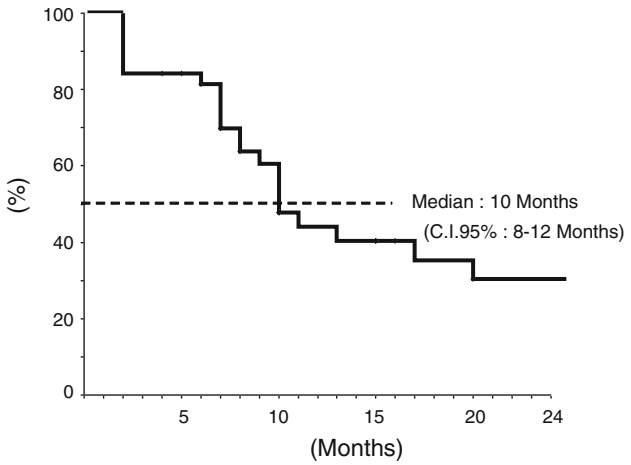

Fig. 1 Progression-free survival of 38 patients receiving IRIS

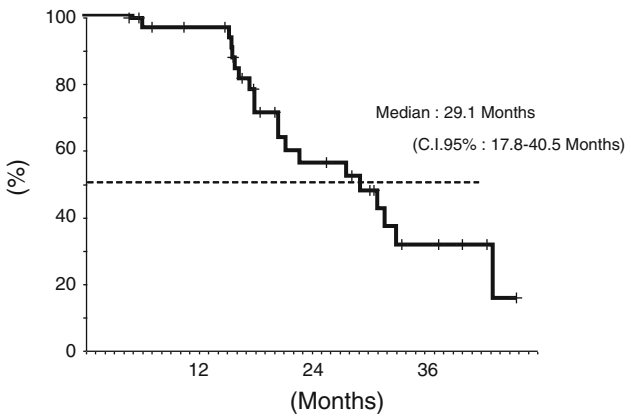

Fig. 2 Overall survival of 38 patients receiving IRIS

were as follows: grade 4 neutropenia and leucopenia, grade 3 anorexia and stomatitis, one patient; grade 4 neutropenia and leucopenia, grade 3 anorexia and diarrhea, one patient; grade 3 neutropenia and leucopenia, grade 3 diarrhea, one patient; grade 3 diarrhea, one patient. On the other hand, the other 34 patients received many courses of this treatment with mild adverse events. Five of 34 patients (14.7%) required dose reduction of either irinotecan or S-1 for management of adverse events. The reasons for reducing the dose of irinotecan or S-1 were as follows: prolonged leucopenia and neutropenia, two patients; diarrhea and anorexia, three patients. All treatment courses were administered on an outpatient basis.

Table 3 Toxicity in all 38 patients during one to four courses

	G1	G2	G3	G4	All grades (%)	Grade ≧ 3 (%)
Hematological toxicities						
Leukopenia	5	13	1	2	55.3	7.9
Neutropenia	8	9	4	2	60.5	15.8
Thrombocytopenia	5	0	1	0	15.8	2.6
Anemia	5	5	1	0	28.9	2.6
Non-hematological toxicities						
Nausea	19	3	3	0	65.8	7.9
Vomiting	3	4	3	0	26.3	7.9
Anorexia	12	5	6	0	60.5	15.8
Stomatitis	3	6	1	0	26.3	2.6
Diarrhea	10	7	4	0	55.2	10.5
General fatigue	8	4	0	0	31.6	0
Abdominal pain	7	0	0	0	18.4	0
Hand- foot syndrome	6	0	0	0	15.8	0
Alopecia	18	3	0	0	55.2	0

Discussion

The aim of this study was to assess the efficacy and safety of the combination therapy of irinotecan and S-1 in patients with previously untreated advanced colorectal cancer. The result of the study indicated that this combination therapy was effective as the first-line chemotherapy for advanced or recurrent colorectal cancer. Recently reported clinical phase II studies of S-1 combined irinotecan therapy are summarized in Table 2. Although differences in study regimens preclude direct comparison, the response rate and median progression-free survival of this study are both consistent with the other regimens of irinotecan and S-1[16–18].

One of the standard chemotherapies for advanced colorectal cancer is the FOLFIRI regimen. The response rates in previous phase III studies of irinotecan with infusional 5-FU and LV ranged from 31 to 62.2% [7–9]. Although

there are limitations in comparing the results of different studies, the response rate (63.1%) and PFS (10.0 months) in the current study were similar to those studies of irinotecan with infusional 5-FU and LV, thus suggesting the same efficacy.

Many oral fluoropyrimidine agents have recently combined irinotecan in place of infusional 5-FU. The main agents were S-1, UFT(uracil/tegafur), and Capecitabine. The combination therapies of irinotecan and these oral agents were reported in the patients with colorectal cancer [16, 17, 19–24]. The combination of capecitabine and irinotecan in patients with advanced colorectal cancer has shown a good response. The response rates ranged 34–50% [20, 22, 23]. On the other hand, UFT/leucoborin combined with irinotecan has also shown high response rates of 20–41.7% [19, 24].

Toxicity was generally mild and manageable on an outpatient basis. The most common treatment-related hematological toxicity was neutropenia. The most common types of non-hematological toxicity were anorexia, nausea, and diarrhea. However, the incidence of grade 3 or 4 anorexia or diarrhea was low. Importantly, there were no treatment-related deaths during the study. Four cases (10.5%) discontinued only one course of this regimen because of grade 3 or 4 anorexia and neutropenia. Once the patients were able to take this treatment without severe adverse events at the initial course, they could continue this regimen many times. The combination of irinotecan and S-1 in patients with advanced colorectal cancer is thus considered to have a manageable toxicity. Yuki et al. reported the frequency of grade 4 neutropenia to be 10%, while grade 3 diarrhea is 15% [18]. Goto et al. [16] has reported the most frequent grade 3/4 adverse events to be neutropenia (15%), anorexia (12.5%), and anemia (7.5%). The current results were similar to those observed with the combination of irinotecan and S-1. The combination of capecitabine and irinotecan in patients with advanced colorectal cancer has been also shown manageable toxicity. The frequent Grade 3/4 adverse events were neutropenia (5–25%) and diarrhea (10–34%) [20–23]. UFT/leucoborin combined with irinotecan has also shown tolerable toxicities. The frequent Grade 3/4 adverse events were neutropenia 13.3–35% and diarrhea 15–16.2% [19, 24]. These results were not inferior to the FOLFIRI regimen in either efficacy or toxicity, thereby suggesting this next new combination therapy with irinotecan for advanced colorectal cancer to possibly be oral fluoropyrimidine in place of infusional 5-FU.

The relative dose intensity of the current regimen was 83.2% of irinotecan and 86.0% of S-1. And response rate was 63.1%. Duration of response in the 5 cases with complete response was 7 to 40 months (median 29 months). Unfortunately, there was no cases in which metastectomy had been done as a result of downstaging. The most important finding in this study is the combination therapy of S-1 plus irinotecan that has good compliance and efficacy for patients with advanced and metastatic colorectal cancer.

Fifteen of 31 patients (48.4%) stopped the combination of irinotecan and S-1 administered FOLFOX ± bevacizumab regimen as the 2nd line therapy. The median overall survival in the current study is good in comparison with the data from larger phase III trials of the IFL [5] and FOLFIRI [7] regimens (17.4, 21.5 months). The reason for the good prognosis might be due to the fact the patients entered into this study were all performance status 0, while almost all demonstrated single organ metastasis (33/38; 86.8%).

In conclusion, it is important to prove that S-1 can replace the established infusional 5-FU plus leucovorin combinations without negatively affecting either efficacy or toxicity. In terms of patient convenience, oral fluoropyrimidine is clearly considered to be advantageous [22]. In particular, the combination therapy of irinotecan and S-1 is a promising regimen, which is considered to offer benefits in both safety and survival.

Conflict of interest None.

References

1. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S (2001) Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 19:3801–3807
2. Sargent DJ, Niedzwiecki D, O'Connell MJ, Schilsky RL (2001) Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. N Engl J Med 345:144–145
3. Meta-analysis Group in Cancer (1998) Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 16:301–308
4. De Gramont A, Bosset JF, Milan C, Rougier P, Bouche O, Etienne PL, Morvan F, Louvet C, Guillot T, Francois E, Bedenne L (1997) 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 15:808–815
5. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. Lancet 355:1041–1047
6. Punt CJA (2004) New options and old dilemmas in the treatment of patients with advanced colorectal cancer. Ann Oncol 15:1453–1459
7. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, De Gramont A (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 22:229–237
8. Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, Carteni G, Agostara B, Pezzella G, Manzione L, Borsellino N, Misino A, Romito S, Durini E, Cordio S, Di Seri M, Lopez M, Maiello E (2005) Phase III randomized trial of FOLFIRI versus

FOLFOX4 in the treatment of advanced colorectal cancer: multicenter study of the Gruppo Oncologico Dell'italia Meridionale. J Clin Oncol 23:4866–4875
9. Kohne CH, Van Cutsem E, Bokemeyer JWC, El-Serafi M, Lutz MP, Lorenz M, Reichardt P, Ruckle-Lanz H, Frickhofen N, Fuchs R, Mergenthaler HG, Langenbuch T, Vanhoefer U, Rougier P, Voigtmann R, Muller L, Genicot B, Anak O, Nordlinger B (2005) Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. J Clin Oncol 23:4856–4865
10. Verso M, Agnelli G (2003) Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol 21:3665–3675
11. Kuter DJ (2004) Thrombotic complication of central venous catheters in cancer patients. Oncologist 9:207–216
12. Shirasaka T, Nakano K, Takechi T, Satake H, Uchida J, Fujioka A, Saito H, Okabe H, Oyama K, Tateda S, Unemi N, Fukushima M (1996) Antitumor activity of 1 M tegafur-0.4 M 5-chloro-2, 4-dihydroxy pyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. Cancer Res 56:2602–2606
13. Hirata K, Horikoshi N, Aiba K, Okazaki M, Denno R, Sasaki K, Nakano Y, Ishizuka H, Yamada Y, Uno S, Taguchi T, Shirasaka T (1999) Parmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. Clin Cancer Res 5:2000–2005
14. Shiozawa M, Sugano N, Tsuchida K, Morinaga S, Akaike M, Sugimasa Y (2009) A phase I study of combination therapy with S-1 and irinotecan (CPT-11) in patients with advanced colorectal cancer. J Cancer Res Clin Oncol 135:365–370
15. 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
16. Goto A, Yamada Y, Yasui H, Kato K, Hamaguchi T, Muro K, Shimada Y, Shirao K (2006) Phase II study of combination therapy with S-1 and irinotecan in patients with advanced colorectal cancer. Ann Oncol 17:968–973
17. Tsunoda A, Yasuda N, Nakao K, Narita K, Watanabe M, Matsui N, Kusano M (2009) Phase II study of S-1 combined with irinotecan (CPT-11) in patients with advanced colorectal cancer. Oncology 77:192–196
18. Yuki S, Komatsu Y, Sogabe S, Iwanaga I, Kudo M, Miyagishima T, Nakamura M, Hatanaka K, Asaka M, Sakata Y (2009) Phase II study of combination with irinotecan and S-1(IRIS) for inoperable recurrent advanced colorectal cancer (HGCSG0302): Final analysis. Gastrointestinal Cancer Symposium. (Abstract No. 463)
19. Mackay HJ, Hill M, Twelves C, Glasspool R, Price T, Campbell S, Massey A, Macham MA, Uzzel M, Bailey SM, Martin C, Cunningham D (2003) A phase I/II study of oral uracil/tegafur (UFT), leucovorin and irinotecan in patients with advanced colorectal cancer. Ann Oncol 14:1264–1269
20. Bajetta E, Di Bartolomeo M, Mariani L, Cassata A, Artale S, Frustaci S, Pinotti G, Bonetti A, Carreca I, Biasco G, Bonaglia L, Marini G, Iannelli A, Cortinovis D, Ferrario E, Baretta E, Lambiase A, Buzzoni R (2004) Randomized multicenter phase II trial of two defferent schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. Cancer 100:279–287
21. Grothey A, Jordan K, Kellner O, Constantin C, Dietrich G, Kroening H, Mantovani L, Schlichting C, Forstbauer H, Schmoll HJ (2004) Capecitabine/irinotecan (CapIri) and capecitabine/oxaliplatin (CapOx) are active second-line protocols in patients with advanced colorectral cancer(ACRC) after failure of first-line combination therapy: results of a randomized phase II study. J Clin Oncol 22:No14S. (abstract3534)
22. Borner MM, Bernhard J, Dietrich D, Popescu R, Wernli M, Saletti P, Rauch D, Herrmann R, Koeberle D, Honegger H, Brauchli P, Lanz D, Roth AD (2005) 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 16:282–288
23. Patt YZ, Lee FC, Leibmann JE, Diamandidis D, Eckhardt SG, Javle M, Justice GR, Keiser W, Salvatore JR, Bexon A, Lin E (2007) Capecitabine plus 3-weekly irinotecan (XELIRI regimen) as first-line chemotherapy for metastatic colorectal cancer: phase II trial results. Am J Clin Oncol 30:350–357
24. Bajetta E, Di Bartolomeo M, Buzzoni R, Mariani L, Zilembo N, Ferrario E, Lo Vullo S, Aitini E, Isa L, Barone C, Jacobelli S, Recaldin E, Pinotti G, Iop A (2007) Uracil/ftorafur/leucovorin combined with irinotecan (TEGAFIRI) or oxaliplatin (TEGAFOX) as first-line treatment for metastatic colorectal cancer patients: results of randomized phase II study. Br J Cancer 96:439–444