Cancer Chemother Pharmacol (2008) 61:83–88
DOI 10.1007/s00280-007-0450-7

ORIGINAL ARTICLE

A phase II trial of modified weekly irinotecan and cisplatin for chemotherapy-naïve patients with metastatic or recurrent squamous cell carcinoma of the esophagus

Dae Ho Lee · Heung Tae Kim · Ji-Youn Han · Sung Young Lee · Sung Jin Yoon · Hyae Young Kim · Jin Soo Lee

Received: 24 October 2006 / Accepted: 26 February 2007 / Published online: 28 April 2007

Abstract
Purpose This phase II study assessed the efficacy and toxicity profile of a modified weekly irinotecan and cisplatin for chemotherapy-naïve patients with metastatic/recurrent esophageal squamous cell carcinoma (SQCC).
Methods The eligibility criteria included histologically confirmed esophageal SQCC, no prior chemotherapy, adequate organ functions and written informed consent. Patients received irinotecan 65 mg/m^2 plus cisplatin 30 mg/m^2 on days 1 and 8, every 3 weeks.
Results Thirty-two patients were assessed for response and toxicity. Ten patients achieved a partial response (31.3%; 95% CI, 16.0–50.0%). With a median follow-up of 19.0 months, median progression-free and overall survival was 4.4 and 9.6 months, respectively, with a 1-year survival rate of 27.4%. Grade (G) 3/4 neutropenia was observed in 50.0% of the patients, which was the most common cause of dose reduction or therapy delay. G3 non-hematologic toxicity included seven (21.9%) asthenias, four (12.5%) diarrheas, and one (3.1%) nausea/vomiting, but no G4 non-hematologic toxicity was observed.
Conclusions This modified weekly irinotecan and cisplatin failed to ameliorate hematologic toxicity and to improve efficacy. However, easy administration and favorable non-hematologic toxicity as well as modest anti-tumor activity against metastatic or recurrent esophageal SQCC can make this regimen a potential treatment option, given the complexity of administration and toxicity of conventional infusional 5-FU and cisplatin.

Keywords Irinotecan · Cisplatin · Esophageal squamous cell carcinoma · Modified schedule

D. H. Lee
Division of Oncology, Department of Internal Medicine, Asan Medical Center, University of Ulsan, Seoul, South Korea

H. T. Kim · J.-Y. Han · S. Y. Lee · S. J. Yoon · H. Y. Kim · J. S. Lee (✉)
Center for Lung Cancer, Research Institute and Hospital, National Cancer Center, 809 Madu-dong, Ilsandong-gu, Goyang, Gyeonggi 411-769, South Korea
e-mail: jslee@ncc.re.kr

Introduction

The prognosis of the patients diagnosed with esophageal cancer is poor with a 5-year-survival rate of less than 15%, in general. At the time of diagnosis, around 80% of the patients already have locally advanced or metastatic disease and approximately 80% of them will die within 1 year. To make it worse, about 85–90% of patients undergoing curative resection for their early-staged disease eventually die of recurrent disease [1]. The combination of cisplatin and continuous-infusion of 5-fluorouracil (5-FU) has been regarded as the standard regimen for squamous cell carcinoma of the esophagus, with a 15–45% response rate in metastatic disease. However, median duration of response is generally short and median survival is only 6–10 months [2], and intravenous infusion schedule of 5-FU often require long-term hospitalization or central venous access and use of an infusional pump if therapy is to be administered as an outpatient. Protracted oral administration of 5-FU prodrugs, such as UFT, capecitabine, and S-1, may be preferable to the patients, but there is as yet not much evidence that these agents have enhanced activity [4, 5].

Among the newer agents, such as taxanes, vinorelbine, and irinotecan, which have shown activity as a single agent [6–8], irinotecan when combined with cisplatin showed very promising activity, particularly against squamous cell

carcinoma of the esophagus [9]. Furthermore, its 4-week on and 2-week off schedule is more useful due to easy administration at outpatient clinics. However, 66% of patients receiving this regimen experienced either delay of treatment by 1 or 2 weeks or shortening of a treatment to 3 weeks from 4 weeks mostly due to hematologic toxicity, leading us to develop a modified schedule to reduce hematologic toxicity and to improve delivery of treatment. Therefore, we conducted phase II trial of a modified 2-week on and 1-week off schedule of irinotecan and cisplatin to determine its toxicity profile and efficacy in chemotherapy-naïve patients with metastatic or recurrent squamous cell carcinoma of the esophagus, postulating that this modified schedule might reduce hematologic toxicity and improve delivery of therapy, but preserve the antitumor activity of a 4-week and 2-week off schedule.

Methods

Eligibility criteria

Patients with metastatic or recurrent squamous cell carcinoma of the esophagus that had been histologically confirmed were eligible. Additional criteria were as follows: (1) age of 18 –75 years, (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (3) bi-dimensionally measurable lesion(s) on computed tomography scan, (4) adequate bone marrow, hepatic, and renal functions, defined as WBC $\geq$ 3,000/mm^3, neutrophils $\geq$ 1,500/mm^3, platelets $\geq$ 100,000/mm^3, hemoglobin $\geq$ 10 mg/dl, alanine aminotransferase or aspartate aminotransferase $\leq$2.5 times the upper normal limit, serum bilirubin $\leq$1.5 mg/dl, and serum creatinine $\leq$ 1.5 mg/dl, (5) neither prior chemotherapy nor molecular-targeted therapy, and (6) no prior radiotherapy to measurable lesion(s) but previous surgery and/or chest radiotherapy for the primary lesion is allowed. Written informed consent approved by the Institutional Review Board of National Cancer Center was obtained from all patients prior to commencing treatment. The study followed the Declaration of Helsinki and good clinical practice guidelines.

Treatment plan and response evaluation

Treatment consisted of irinotecan 65 mg/m^2 and cisplatin 30 mg/m^2 given weekly for 2 weeks followed by 1-week rest period at outpatient clinic, and was repeated every 3 weeks until disease progression, unacceptable toxicity or patient's refusal. Prior to study entry, all patients provided a complete history including performance status and concomitant medication, and underwent a physical examination. Laboratory studies included a complete blood count with differential, liver and renal function tests, and uninalysis. A chest computed tomographic scan including upper abdomen was required within 4 weeks of initiation therapy.

Dose modification for toxicity was based on worst toxicity observed after the preceding treatment; in the presence of multiple toxicities, the specified greater dose reduction was implemented. Full dose therapy was given if patients had an absolute neutrophil count (ANC) $\geq$1,500/mm^3, platelets $\geq$75,000/mm^3, and no grade 2 or more non-hematologic toxicity. Patients who had an ANC $\geq$1,000/mm^3 but <1500/mm^3, or platelets $\geq$50,000/mm^3 but <75,000/mm^3 , or experienced grade 2 toxicity continued on therapy but were reduced by one dose level (to irinotecan 55 mg/m^2 and cisplatin 20 mg/m^2). If patient could not receive treatment on day 8, one evaluated again on day 10 and resumed the treatment as per above. If ANC <1,000, or platelet <50,000 or grade 3 or 4 toxicity on day 10, the treatment was omitted. Treatment could be delayed for up to 2 weeks to allow a patient sufficient time to recover from therapy-related toxicity.

All patients were routinely given oral alkalization and defecation control treatment to prevent irinotecan-induced diarrhea starting on the first day of irinotecan infusion and for a total of 4 days, which consisted of sodium bicarbonate 500 mg and magnesium oxide 500 mg after every meal and before bed time for a total of four doses a day; ursodeoxycholic acid 100 mg after every meal for three doses a day; and basic water (pH greater than 7.2) 1,500–200 ml for a day. In order to prevent constipation and permit defecation at least once a day, all patients were given magnesium oxide up to a total dose of 4,000 mg/day and basic water up to a total dose of 2,000 ml/day, but those who experienced watery diarrhea discontinued till the symptom resolved [10]. Cholinergic symptoms that occurred during or within 1 h after irinotecan administration were treated with atropine 1 mg or as needed. Loperamide was provided as therapy for delayed diarrhea with the instruction that at the first indication of diarrhea (i.e., first poorly formed or loose stool or first episode of one to two or more bowel movements than usual in a day) that occurred more than 12 h after irinotecan administration, a patient begins to take loperamide in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 h, round the clock until diarrhea stops for at least 12 h.

The primary end point of the study was objective tumor response rate, which was assessed according to the WHO criteria after every three cycles by computed tomography scans [11]. Complete response (CR) involved the complete disappearance of all clinical and radiologic evidence of disease. Partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the maximal perpendicular dimensions of measurable lesions without the appearance of any new lesions or progression of any existing lesions. Progressive disease (PD) was defined as

any of the following; a ≥25% increase in the sum of the products of all measurable lesions, the appearance of new lesions, progression of any existing lesions, or failure to return for evaluation because of deterioration. Stable disease (SD) was defined as a tumor response that did not meet the criteria for CR, PR, or PD. Patients were evaluated for toxicity using the National Cancer Institute Common Toxicity Criteria version 2.0 [12].

Statistical consideration

Simon's two-stage mini-max design was used to determine the sample size and decision criteria for this phase II study [13]. With the target activity level of 50% and the lowest RR of interest set at 25%, we needed 33 patients with a 90% power to accept the hypothesis and a 5% significance level to reject the hypothesis. If four or fewer responses in the first 16 patients are observed, the study is stopped early. If 12 or fewer responses are observed by the end of the study, no further investigation of the drug is warranted. The overall response rate was calculated using all enrolled patients, and a 95% confidence interval (CI) was calculated using exact methods. Duration of response for responders was defined as the interval between the date of documented response and the date of documented disease progression. Progression-free survival was defined as the interval between the date of start of the treatment and the date of documented disease progression or death from any cause. Overall survival was also defined as the interval between the date of start of the treatment and the date of death due to any cause. If a patient was lost to follow-up, that patient was censored at the last date of contact. All time-to-event variables were analyzed using Kaplan–Meier product-limit survival estimates. Dose intensity was calculated using the method of Hryniuk and Bush [14]. Data were updated as of September 30, 2006.

Results

Patient characteristics

Between June 2003 and June 2006, a total of 32 patients were enrolled and the patients' characteristics are shown in Table 1. Ten patients had received prior curative surgery and of these, three patients received radiotherapy to chest as post-operative adjuvant therapy (2) and curative therapy for local recurrence (1).

Objective responses and survival outcomes

Of the 32 assessable patients, 10 achieved objective responses (all PR) for an overall response rate of 31.3% (95% confidence interval [CI], 16.1–50.0%) (Table 2). The median duration of response was 5.3 months (95% CI, 3.6–7.0 months). With a median follow-up time of 19.0 months, the median progression-free survival and survival time was 4.4 and 9.6 months, respectively, with a 1-year survival rate of 27.1% (95% CI, 10.2 to 44.8%) (Fig. 1).

Table 1 Patients' characteristics

Characteristic	No. of patients	%
Total patients	32	
Age (years)		
Median	64	
Range	44–72	
Sex		
Male	31	(96.9)
Female	1	(3.1)
ECOG status		
Grade 0	10	(31.3)
Grade 1	19	(59.4)
Grade 2	3	(10.3)
Prior therapy		
No prior therapy	22	(68.8)
Prior surgery	10	(31.3)
Prior chest radiotherapy	3	(6.9)

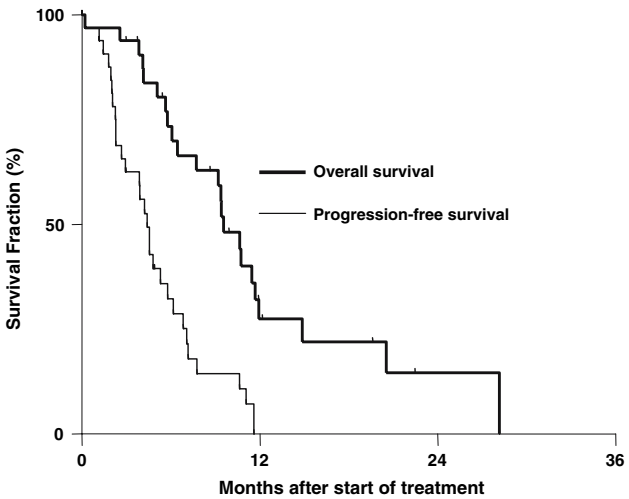

Fig. 1 Progression-free and overall survival. Tick marks indicate censored data

Table 2 Best overall tumor response according to WHO Criteria

Response	No. of patients	% (95% CI)
PR	10	31.3 (16.1–50.0)
SD	11	34.4 (18.6–53.2)
PD	11	34.4 (18.6–53.2)
Total	32	100

Treatment cycles administered

Table 3 lists the number of treatment cycles delivered. A total of 167 cycles was administered with the median of 5 cycles, (range 1–12 cycles). Dose reduction and therapy-delay occurred in 30 cycles (20.0%) and 68 cycles (40.7%), respectively, mainly due to hematologic toxicity. The median dose intensity was 34.4 mg/m^2/week (79.4% of planned dose of 43.3 mg/m^2/week) for irinotecan and 15.4 mg/m^2/week (77.1% of planned dose of 20.0 mg/m^2/week) for cisplatin, respectively. The main reason for discontinuation of treatment was disease progression (75.0%), but 7 of 19 patients receiving more than four cycles had to discontinue treatment due to toxicity, mainly prolonged hematologic toxicity.

Table 3 Treatment administration and reasons for discontinuation

Variables	No. of patients (n = 32)	(%)
No. of cycles delivered		
1	1	3.1
2	3	9.4
3	9	28.1
4	3	9.4
5	2	6.3
6	10	31.2
9	2	6.3
11	1	3.1
12	1	3.1
Reasons for treatment discontinuation		
Under treatment	1	3.1
Disease progression	24	75.0
Toxicity	7	21.9

Toxicity

Toxicity profile for all 32 patients is shown in Table 4. Sixteen patients (50.0%) experienced grade 3 or 4 neutropenia, although only three patients (9.4%) had febrile neutropenia requiring hospitalization. Grade 3 diarrhea occurred in four patients (12.5%). One patient died of tumor bleeding after receiving treatment on day 1 of the first cycle, which was not deemed treatment-related death.

Salvage chemotherapy on progression

Of the 30 patients who had disease progression, 18 received second-line chemotherapy after first-line irinotecan/cisplatin therapy. The second-line chemotherapy regimens administered included taxanes or 5-FU agents, or combination of both agents. One patient received gefitinib, but did not respond to it. Two (14.3%) of 14 evaluable patients responded to second-line chemotherapy, while seven patients receiving third- and fourth-line chemotherapy did not respond to chemotherapy at all.

Discussion

Disappointingly, our modified 2-week on and 1-week off schedule of weekly irinotecan and cisplatin failed to ameliorate the hematologic toxicity and to improve delivery of therapy and survival outcome, compared with

Table 4 Toxicity profile

Adverse effect	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicity—no. of patients (%)					
Leukopenia	3 (9.4)	11 (34.4)	10 (31.3)	6 (18.8)	2 (6.3)
Neutropenia	2 (6.3)	2 (6.3)	12 (37.5)	10 (31.3)	6 (18.8)
Anemia	1 (3.1)	6 (18.8)	15 (46.9)	9 (28.1)	1 (3.1)
Thrombocytopenia	15 (46.9)	11 (34.4)	4 (12.5)	2 (6.3)	0 (0.0)
Non-hematologic toxicity—no. of patients (%)					
Asthenia	2 (6.3)	8 (25.0)	15 (46.9)	7 (21.9)	0 (0.0)
Alopecia	10 (31.3)	12 (37.5)	10 (31.3)	–	–
Anorexia	7 (21.9)	11 (34.4)	14 (43.8)	0 (0.0)	0 (0.0)
Constipation	24 (75.0)	4 (12.5)	3 (9.4)	1 (3.1)	0 (0.0)
Diarrhea	13 (40.6)	14 (43.8)	1 (3.1)	4 (12.5)	0 (0.0)
Nausea/vomiting	10 (31.3)	12 (37.5)	9 (28.1)	1 (3.1)	0 (0.0)
Elevated AST/ALT	24 (75.0)	7 (21.9)	1 (3.1)	0 (0.0)	0 (0.0)
Elevated bilirubin	27 (84.4)	2 (6.3)	3 (9.4)	0 (0.0)	0 (0.0)
Elevated creatinine	20 (62.5)	11 (34.4)	1 (3.1)	0 (0.0)	0 (0.0)
Febrile neutropenia	29 (90.6)	–	–	3 (9.4)	–
Neuropathy	23 (71.9)	7 (21.9)	1 (3.1)	1 (3.1)	0 (0.0)

Table 5 Comparison of different doses and schedules of Irinotecan and Cisplatin

Study	Tumor	Objective tumor response	G3/4 neutropenia	G3/4 diarrhea
Ilson et al.[9] Irinotecan 65 mg/m^2 D1,8,15,22 cisplatin 30 mg/m^2 D1,8,15,22 Q 6 weeks	Esophageal cancer	20/35 (57%)	14/31 (46%)	4/30 (11%)
Ilson et al. [15] Irinotecan 65 mg/m2 D1,8 cisplatin 30 mg/m2 D1,8 Q 3 weeks	Esophageal cancer	10/28 (36%)	8/31 (22%)	7/31 (19%)
Lee et al. (Current) Irinotecan 65 mg/m2 D1,8 cisplatin 30 mg/m2 D1,8 Q 3 weeks	Esophageal cancer	10/32 (31%)	16/32 (48%)	4/32 (12%)
Noda et al. [16] Irinotecan 60 mg/m2 D1,8,15 cisplatin 60 mg/m2 D1 Q 4 weeks	Small cell lung cancer	65/77 (84%)	49/75 (65%)	12/75 (16%)
Pozzo et al. [17] Irinotecan 200/m2 D1 cisplatin 60 mg/m2 D1 Q 3 weeks	Gastric or gastro−esophageal junction cancer	18/72 (25%)	46/72 (66%)	13/72 (18%)
Han et al. [18] Irinotecan 80 mg/m2 D1,8 cisplatin 60 mg/m2 D1 Q 3 weeks IP; irinotecan first given PI: CDDP first given	Non-small cell lung cancer	36/77 (47%) IP;5/38 (39%) PI; 21/39 (54%)	58/80 (72%) IP:30/39 (77%) PI:28/41 (69%)	21/80 (26%) IP:12/39 (31%) PI:9/41 (22%)

4-week on and 2-week off schedule. Other trials of different doses and schedules of both agents also showed similar toxicity profile (Table 5) [9, 15–18]. In addition, the trials of docetaxel and irinotecan combination showed a similar result that the weekly schedule appears less active than the every three-week dosing schedule [19, 20]. Therefore, further trials to find the optimal dose and schedule of irinotecan and cisplatin combination seem unlikely to exceed the limit that can be achieved in the current study.

In the current study, we observed modest anti-tumor activity with a response rate of 31.3% and median survival of 9.4 months, which was comparable to most commonly used 5-FU and cisplatin combination with response rates of 20 to 50% and median survival of 6 to 8 months, although this was a single institution phase II study in which patient selection might play a significant role [21–23]. Despite a 50% rate of grade 3 or 4 neutropenia, febrile neutropenia occurred in less than 10% and our modified irinotecan and cisplatin combination had favorable non-hematologic toxicity profile. In terms of the dose-intensity, we could also reduce starting dose of therapy in an attempt to ameliorate further toxicity, especially for those who had poor performance or comorbid disease. Of note, grade 3 diarrhea developed in only four patients (12.5%), which might be partly due to routine oral alkalization and defecation control, and the routine anti-diarrheal medications can be more beneficial to prevent irinotecan-induced diarrhea.

Multimodality therapy has been employed for treatment of locally advanced esophageal cancer. And, molecularly targeted therapies, such as angiogenesis inhibitors or epidermal growth factor receptor blockers, have already entered clinical practice based on their favorable toxicity profile as well as anti-tumor activity. Although, no randomized trials are available, this regimen also showed promising results, when combined with not only radiotherapy [24–27] but also molecularly targeted drugs [28, 29]. Therefore, this regimen can be used at outpatient clinic in conjunction with radiotherapy, molecularly targeted agents, or both.

In conclusion, this modified weekly irinotecan and cisplatin combination chemotherapy failed to ameliorate the hematologic toxicity and to improve efficacy, but still had modest anti-tumor activity and survival outcome comparable to that of current chemotherapeutic regimens. In addition, considering better non-hematologic toxicity profile and easier administration at outpatient clinic, we can use this regimen as one of the treatment options in patients with metastatic or recurrent squamous cell carcinoma of the esophagus.

Acknowledgment Supported in part by NCC Grant 0510140 from National Cancer Canter. Irinotecan (Campto®) was kindly provided by CJ Corp., Seoul, Korea. Presented partly in Poster Session at the 31st European Society for Medical Oncology Congress, Istanbul, Turkey, September 29–October 3, 2006.

References

1. Stewart BW, Kleihues P (2003) World cancer report. IARC Press Lyon, France
2. Ilson DH (2003) Oesophageal cancer: new developments in systemic therapy. Cancer Treat Rev 29:525–532
3. Ajani JA, Ilson DH, Daugherty K, Pazdur R, Lynch PM, Kelsen DP (1994) Activity of Taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 86:1086–1091
4. Seymour MT, Dent JT, Papamichael D, Wilson G, Cresswell H, Slevin ML (1999) Epirubicin, cisplatin and oral UFT with leucovorin ('ECU'): a phase I-II study in patients with advanced upper gastrointestinal tract cancer. Ann Oncol 10:1329–1333
5. Lee J, Im Y, Kang J, E Nam, Lee S, Park J, Park Y, Kang W, Park K (2005) Phase II study of capecitabine and cisplatin as first-line therapy in patients with recurrent or metastatic esophageal carcinoma. J Clin Oncol 2005 ASCO Ann Meet Proc 23(16S):4221
6. Conroy T, Etienne PL, Adenis A, Wagener DJ, Paillot B, Francois E, Bedenne L, Jacob JH, Seitz JF, Bleiberg H, Van Pottelsberghe C, Van Glabbeke M, Delgado FM, Merle S, Wils J (1996) Phase II trial of vinorelbine in metastatic squamous cell esophageal carcinoma. J Clin Oncol 14:164–170
7. Muhr-Wilkenshoff F, Hinkelbein W, Ohnesorge I, Wolf KJ, Riecken EO, Zeitz M, Scherubl H (2003) A pilot study of irinotecan (CPT-11) as single-agent therapy in patients with locally advanced or metastatic carcinoma. Int J Colorectal Dis 18:330–334
8. Muro K, Hamaguchi T, Ohtsu A, Boku N, Chin K, Hyodo I, Fujita H, Takiyama W, Ohtsu T (2004) A phase II study of single agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol 15:955–959
9. Ilson DH, Saltz L, Enzinger P, Huang Y, Komblith A, Gollub M, O'Reilly E, Schwartz G, DeGroff J, Gonzalez G, Kelsen DP (1999) A phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 17:3270–3275
10. Takeda Y, Kobayashi K, Akiyama Y, Soma T, Handa S, Kudoh S, Kudo K (2001) Prevention of irinotecan (CPT-11)-induced diarrhea by oral alkalization combined with control of defecation in cancer patients. Int J Cancer 92:269–275
11. World Health Organization (1979) Handbook for REPORTING RESULTS OF CANCER TREATMENt (WHO Offset Publication No. 48). World Health Organization, Geneva
12. National Cancer Institute. (1999) The revised common toxicity criteria:Version 2.0. CTEP Website. http://www.ctep.info.nih.gov (30 September 2006, date last assessed)
13. Simon R. (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trial 10:1–10
14. Hryniuk W, Bush H (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2:1281–1288
15. Ilson DH (2004) Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 18(Suppl 14):22–25
16. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, Fukuoka M, Mori K, Watanabe K, Tamura T, Yamamoto S, Saijo N; Japan Clinical Oncology Group (2002) Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85–91
17. Pozzo C, Barone C, Szanto J, Padi E, Peschel C, Bukki J, Gorbunova V, Valvere V, Zaluski J, Biakhov M, Zuber E, Jacques C, Buqat R (2004) Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study. Ann Oncol 15:1773–1781
18. Han JY, Lim HS, Lee DH, Ju SY, Lee SY, Kim HY, Park YH, Park CG, Lee JS (2006) Randomized Phase II study of two opposite administration sequences of irinotecan and cisplatin in patients with advanced non-small cell lung carcinoma. Cancer 106:873–880
19. Jatoi A, Tirona MT, Cha SS, Alberts SR, Rowland KM, Morton RF, Nair S, Kardinal CG, Stella PJ, Mailliard JA, Sargen D, Goldberg RM (2002) A phase II trial of docetaxel and CPT-11 in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction, and gastric cardia. Int J Gastrointest Cancer 32:115–123
20. Lordick F, von Schilling C, Bernhard H, Hennig M, Bredenkamp R, Peschel C (2003) Phase II trial of irinotecan plus docetaxel in cisplatin-pretreated relapsed or refractory oesophageal cancer. Br J Cancer 89:630–633
21. Ajani JA (1994) Contribution of chemotherapy in the treatment of carcinoma of the esophagus: results and commentary. Semin Oncol 21:474–482
22. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M (1997) Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 15:261–267
23. Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, Bedenne L, Namer M, De Besi P, Gay F, Collette L, Sahmoud T (1997) Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 33:1216–1220
24. Ilson DH, Banis M, Kelsen DP, O'Reilly E, Karpeh M, Coit D, Rusch V, Gonen M, Wilson K, Minsky BD (2003) Phase I trial of escalating-dose irinotecan given weekly with cisplatin and concurrent radiotherapy in locally advanced esophageal cancer. J Clin Oncol 21:2926–2932
25. Ilson DH, Minsky B, Kelson D (2002) Irinotecan, cisplatin, and radiation in esophageal cancer. Oncology (Williston Park) 16(suppl 5):11–15
26. Michel P, Adenis A, Di Fiore F, Boucher E, Galais MP, Dahan L, Mirabel X, Hamidou H, Raoul JL, Jacob JH, Hellot MF, Prod'Homme S, Paillot B (2006) Induction cisplatin-irinotecan followed by concurrent cisplatin-irinotecan and radiotherapy without surgery in oesophageal cancer: multicenter phase II FFCD trial. Br J Cancer 95:705–709
27. Visbal AL, Darling G, Wong R, Guindi M, Hornby J, Feld R, Ringash J, Keshavjee S, Chen E, Brierly J, Knox J (2006) Phase II trial of preoperative (POP) irinotecan (I) + cisplatin (C) and radiotherapy for esophageal cancer. J Clin Oncol 2006 ASCO Ann Meet Proc 24(18S):4056
28. Enzinger PC, Yock T, Suh W, Fidias P, Mamon H, Choi N, Lehman N, Lawrence C, Lynch T, Fuchs C (2006) Phase II cisplatin, irinotecan, cetuximab and concurrent radiation therapy followed by surgery for locally advanced esophageal cancer. J Clin Oncol 2006 ASCO Ann Meet Proc 24(18S):4064
29. Shah MA, Ramanathan RK, Ilson DH, Levnor A, D'Adamo D, O'Reilly E, Tse A, Trocola R, Schwartz L, Capanu M, Schwartz GK, Kelsen DP (2006) Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 24:5201–5206