Cancer Chemother Pharmacol (2009) 63:427–432
DOI 10.1007/s00280-008-0752-4

ORIGINAL ARTICLE

Phase II trial of biweekly paclitaxel plus infusional 5-fluorouracil and leucovorin in patients with advanced or recurrent inoperable gastric cancer

Hyo Jin Lee · Do Yeun Cho · Ji Chan Park · Sang Byung Bae · Kyu Taek Lee · In Sung Cho · Chang Soon Han · Suk Young Park · Hwan Jung Yun · Samyong Kim

Received: 4 January 2008 / Accepted: 26 March 2008 / Published online: 16 April 2008

Abstract
Purpose To investigate the efficacy and safety of combination chemotherapy with biweekly paclitaxel plus infusional 5-fluorouracil and leucovorin in the treatment of patients with advanced or metastatic gastric cancer.
Patients and methods Chemonaive patients with histologically confirmed advanced or recurrent inoperable gastric cancer were enrolled in the present study. Treatment consisted of paclitaxel (75 mg/m^2) and leucovorin (40 mg/m^2) as a 2-h intravenous infusion, followed by 5-fluorouracil (2,400 mg/m^2) as a 46-h continuous infusion. Cycles were repeated every 2 weeks.
Results Thirty patients were enrolled in this study. There were 12 partial responses, giving an overall response rate of 40.0%. At a median follow-up of 10.6 months, the median time to progression and median overall survival were 3.9 and 8.8 months, respectively. The most common hematological toxicity was grade 1–2 anemia, which was seen in 83.3% of patients. No grade 4 leukopenia, thrombocytopenia, or anemia was noted. The most common non-hematological toxicity was anorexia, which was seen in 70% of patients, although grade 3 anorexia was noted in only 10% of cases. There was no severe treatment-related morbidity or death.
Conclusion Combination chemotherapy consisting of biweekly paclitaxel plus infusional 5-fluorouracil and leucovorin was effective and well tolerated in patients with advanced gastric cancers.

Keywords Gastric cancer · Paclitaxel · 5-Fluorouracil · Leucovorin · Biweekly

H. J. Lee · H. J. Yun · S. Kim (✉)
Division of Hematology/Oncology,
Department of Internal Medicine,
Chungnam National University Hospital,
640 Daesa-dong, Jung-gu, Daejeon, South Korea
e-mail: firkim@cnu.ac.kr

D. Y. Cho
Department of Internal Medicine,
Konyang University Hospital, Daejeon, South Korea

J. C. Park · S. Y. Park
Department of Internal Medicine,
Daejeon St. Mary's Hospital, Daejeon, South Korea

S. B. Bae · K. T. Lee
Department of Internal Medicine,
Soon Chun Hyang University Cheonan Hospital,
Cheonan, South Korea

I. S. Cho
Department of Internal Medicine,
Eulji University Hospital, Daejeon, South Korea

C. S. Han
Department of Internal Medicine,
Cheongju St. Mary's Hospital, Cheongju, South Korea

Introduction

Despite a decreasing incidence in many developed countries, gastric cancer is the second leading cause of cancer death worldwide and is the most common malignant tumor in Korea [1–3]. The prognosis of this disease is generally poor with an overall 5-year survival rate of approximately 20% in most countries. The median survival time in patients with advanced or metastatic disease receiving the best supportive care is only 3–5 months [1, 4]. In the past several decades, various chemotherapy regimens have been introduced, and have shown an objective response rate of approximately 20–60% in the treatment of advanced gastric cancer. However, median overall survival remains between

6 and 9 months, and significant treatment-related toxicities are usually inevitable [5, 6]. New treatments with a better therapeutic index are needed to improve the clinical outcome of this disease.

Infusional high-dose 5-fluorouracil (5-FU) has been shown to be an effective and well-tolerated treatment for patients with gastric cancer, and has provided a good base for combination chemotherapy regimens [7–10]. Paclitaxel, an antimitotic agent that binds preferentially to microtubules, has demonstrated activity against gastric cancers in vitro [11, 12]. When administered alone, paclitaxel showed a 20–23% objective response rate in patients with advanced gastric cancer [13, 14]. In addition, paclitaxel acts synergistically with 5-fluorouracil in a sequence-dependent manner. Thus, paclitaxel followed by 5-fluorouracil was highly synergistic, while pre-exposure to 5-fluorouracil followed by paclitaxel resulted in marked antagonism [15, 16]. The non-overlapping toxicity profile of paclitaxel and infusional 5-fluorouracil, and the schedule-dependent synergism between these drugs against human gastric cancer cells [15, 16] suggest the potential value of investigation of such a combination in the treatment of patients with advanced gastric cancer. We conducted a phase II trial of combination chemotherapy with biweekly paclitaxel plus infusional 5-FU and leucovorin to determine the efficacy and toxicity of this regimen in this patient group.

Patients and methods

Eligibility

Patients with histologically confirmed advanced or recurrent inoperable gastric cancer were considered eligible for the study if they fulfilled all of the following criteria: at least one measurable lesion; age >18 and <75 years; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2; life expectancy $\geq$3 months; adequate bone marrow, hepatic, and renal function; no prior radiotherapy or palliative chemotherapy; no concurrent uncontrolled medical condition; no other malignancies (with the exception of basal or squamous cell carcinoma of the skin, treated by surgery); and written informed consent approved by the local Ethics Committees of participating centers. Previous adjuvant chemotherapy was allowed if more than 6 months had elapsed between the end of adjuvant therapy and first relapse. Patients who were pregnant or breast-feeding were excluded from the study.

Treatment and toxicity assessment

Chemotherapy consisted of paclitaxel (Paxel™; Hanmi Pharm. Co., Ltd. Seoul, Korea) at 75 mg/m^2 and leucovorin at 40 mg/m^2 as a 2-h intravenous infusion, followed by 5-fluorouracil at 2,400 mg/m^2 as a 46-h continuous infusion. Cycles were repeated every 2 weeks. Treatment was continued for up to 24 weeks unless the disease progressed, unacceptable toxicity developed, or the patient refused continued treatment. Toxicity was assessed before starting each 2-week cycle according to the National Cancer Institute Common Toxicity Criteria version 3.0. Treatment delay and dose modification were based on the worst adverse effects observed during the previous cycle.

Assessment of response

Responses were classified according to World Health Organization (WHO) criteria. Complete response was defined as the disappearance of all known lesions and absence of new lesions; partial response as a reduction of 50% or more in the sum of the product of the two-dimensional measures of all known lesions and the absence of new lesions; stable disease as a reduction of <50% or an increase <25% in the sum of the product of the two-dimensional measures of all known lesions and the absence of new lesions; and progressive disease as an increase >25% in the two-dimensional measures of one or more known lesions or as the appearance of at least one new lesion. Computed tomography (CT) scans of measurable lesions were performed within 2 weeks prior to starting chemotherapy and were repeated every four cycles (8 weeks). Responses were confirmed by subsequent CT scans at 4–6 weeks after documentation of an initial response. Patients who discontinued participation in the study were evaluated at least every 2 months. Patients were considered assessable for response if they had early disease progression or had received at least four cycles of treatment with at least one tumor assessment. The primary end point of the study was the overall response rate; secondary end points were toxicity, time to progression, and overall survival. The time to progression was defined as the duration from the date of starting treatment to the date of confirmed disease progression or of death by any cause. Overall survival was defined as the duration from the date of starting treatment to the date of death.

Statistical analyses

Simon's optimal two-stage design was used. The response rates of interest were $P_0 = 30\%$ and $P_1 = 50\%$. If there were more than 4 responses in 13 patients in the first stage, the study would continue to a total of 30 patients in the second stage. If there were more than 11 responses in 30 patients in the second stage, this treatment regimen would be acceptable with α of 0.10 and β of 0.10. The Kaplan–Meier method was used for all survival analyses.

Results

Patient characteristics

Between November 2004 and August 2006, 30 patients were enrolled into the study from 6 medical centers. The major clinicopathological characteristics of patients are summarized in Table 1. The median age of the patients was 62 years (range 42–71 years) including 23 men and 7 women, and the majority of patients (63.3%) had a performance status of 1 according to the ECOG scale. Metastatic disease was present in the majority of the study population (29 of 30 patients); liver (19 of 30 patients, 63.3%) and lymph nodes (16 of 30, 53.3%) were the most common sites of metastases.

Efficacy

All 30 patients were evaluable for tumor responses. There were no cases of complete response. Twelve patients achieved a partial response, giving an overall response rate of 40% (95% confidence interval (CI), 24.6–57.7). Stable disease was obtained in ten patients (33.3%; 95% CI 19.2–51.2) and progressive disease was observed in eight patients (26.7%; 95% CI 14.2–44.5). Therefore, the overall disease control rate was 73.3% (22 of 30 patients; 95% CI 55.6–85.8). Of 12 responses, 10 (83.3%) were observed after 4 cycles and 2 (16.7%) after eight cycles of chemotherapy. All patients were included in the survival analysis on an intent-to-treat basis. The median follow-up period was 10.6 months (range 2.7–29.3 months). At the time of analysis (31 July 2007) the median time to progression and overall survival were 3.9 months (range 1.0–8.8 months) and 8.8 months (range 2.7–29.3 months), respectively. The Kaplan–Meier estimated time to progression and overall survival curve are shown in Figs. 1 and 2, respectively.

Table 1 Clinicopathological features of the patients

Number of patients	30
Age (years), median (range)	62 (42–71)
Gender, *n* (%)	
Male	23 (76.7)
Female	7 (23.3)
ECOG performance status, *n* (%)	
0	4 (13.3)
1	19 (63.3)
2	7 (23.3)
Treatment for primary tumor, *n* (%)	
No prior therapy	22 (73.3)
Surgery only	3 (10.0)
Surgery and adjuvant chemotherapy	5 (16.7)
Disease status, *n* (%)	
Locally advanced	1 (3.3)
Metastatic	29 (96.7)
Disease sites, *n* (%)	
Liver	19 (63.3)
Peritoneum	4 (13.3)
Lymph nodes	16 (53.3)
Bone	2 (6.7)
Lung	1 (3.3)
Others	5 (16.7)

ECOG, Eastern Cooperative Oncology Group. Because of rounding, not all percentages total 100

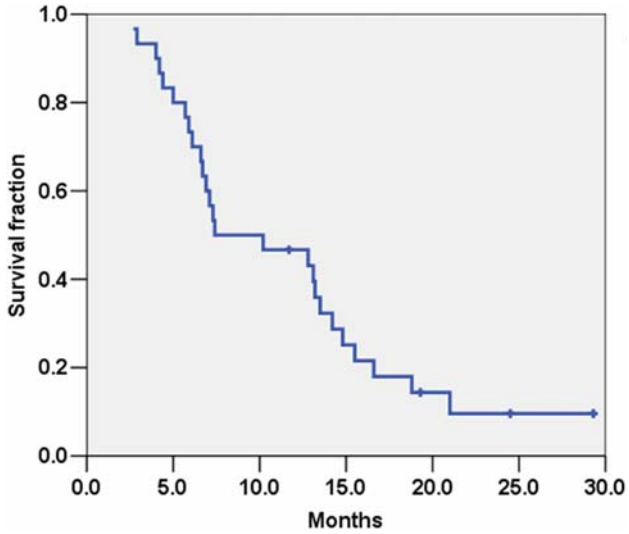

Fig. 1 Kaplan–Meier curve for overall survival of the all patients

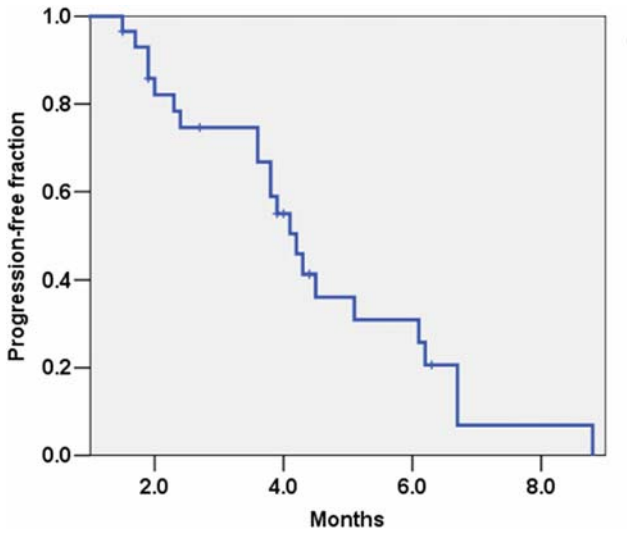

Fig. 2 Kaplan–Meier curve for time to progression of the all patients

Toxicity

A total of 212 cycles were administered, with a median of 8 cycles per patient (range 1–12 cycles). The occurrence and the incidence of toxicities are shown in Table 2. No cases of grade 4 toxicity were observed. The most common toxicities were gastrointestinal. Grade 1 and 2 anorexia, nausea/vomiting, diarrhea, and stomatitis were reported in 60.0, 50, 33.3, and 6.7% of cases in the study population, respectively. Grade 3 anorexia, nausea/vomiting, and stomatitis were recorded in only 10.0, 10.0, and 3.3% of cases, respectively. Severe hematological toxicity was uncommon. Grade 3 anemia, leukopenia, and thrombocytopenia were noted in 6.7, 3.3, and 0% of patients, respectively. Mild to moderate alopecia was observed in 43.4% of cases (grade 1 in 26.7% and grade 2 in 16.7%). There were no febrile neutropenia or treatment-related deaths in this series.

Discussion

The results of this study indicated that biweekly paclitaxel plus infusional 5-fluorouracil and leucovorin is an active combination chemotherapy regimen for patients with inoperable advanced or recurrent gastric cancer, providing excellent tolerability. The overall response rate of 40.0% (95% CI 24.6–57.7%) and median overall survival of 8.8 months (range 2.7–29.3 months) were within the ranges achieved by previously reported major protocols, such as 5-fluorouracil and cisplatin (FP) [17], 5-fluorouracil, leucovorin, and cisplatin (FLP) [18], 5-fluorouracil, doxorubicin, and mitomycin C (FAM) [17, 19, 20], 5-fluorouracil, doxorubicin, and methotrexate (FAMTX) [20], epirubicin, cisplatin, and 5-fluorouracil (ECF) [21], etoposide, leucovorin, and 5-fluorouracil (ELF) [22], etoposide, doxorubicin, and cisplatin (EAP) [23], and oxaliplatin-based regimens [24, 25], in which the objective response rates and median overall survivals ranged from 25 to 64% and from 5.5 to 11 months, respectively [17–25].

Paclitaxel shows good activity against advanced gastric cancer using different administration schedules and various combination regimens with other chemotherapeutic agents [5, 6]. Single-agent paclitaxel regimens, using 3- and 24-h infusion, produced response rates of 8 and 20%, respectively, in the treatment of advanced gastric cancer [26]. In combination with 5-fluorouracil and/or platinum compounds, response rates ranging from 32 to 65.5% were reported in several trials conducted in different settings [27–34]; some delivered paclitaxel weekly, others every 3 weeks; some introduced cisplatin or carboplatin in combination with paclitaxel and 5-fluorouracil, or used oral fluoropyrimidine; some studied chemonaive patients and/or previously treated patients. Relatively high incidences (14–45%) of grade 3 or 4 neutropenia were significant adverse effects in these studies [27–30, 33, 34], which can result in treatment-related morbidity or mortality, thereby compromising the patients' quality of life and increasing medical costs.

Recently, Zhou et al. [35] and Feng et al. [36] reported that biweekly paclitaxel (75 and 90 mg/m^2, respectively) with infusional 5-fluorouracil and leucovorin showed an encouraging response rate of about 65% and only mild toxicity. These results suggested a role for low-dose biweekly paclitaxel-based protocols in patients with advanced gastric cancer, although their studies were performed in small populations and/or within a single institution. In our multicenter prospective study, biweekly paclitaxel with infusional

Table 2 Severity and incidence of toxicity

	Maximum toxicity grades observed for each patient during the study period using NCI-CTC version 3.0			
	1	2	3	4
Anorexia	11 (36.7%)	7 (23.3%)	3 (10.0%)	0
Nausea/vomiting	8 (26.7%)	7 (23.3%)	3 (10.0%)	0
Diarrhea	4 (13.3%)	6 (20.0%)	0	0
Stomatitis	2 (6.7%)	0	1 (3.3%)	0
Dizziness	1 (3.3%)	0	0	0
Alopecia	8 (26.7%)	5 (16.7%)	0	0
Skin rash	1 (3.3%)	0	0	0
Neuropathy	1 (3.3%)	0	0	0
Anemia	7 (23.3%)	18 (60.0%)	2 (6.7%)	0
Leukopenia	3 (10.0%)	4 (13.3%)	1 (3.3%)	0
Thrombocytopenia	1 (3.3%)	0	0	0
Infection	0	4 (13.3%)	0	0

NCI-CTC National Cancer Institute Common Toxicity Criteria

5-fluorouracil and leucovorin showed a modest response rate and median overall survival time comparable to those achieved by previously reported paclitaxel-based weekly or 3-weekly regimens [27–30]. In addition, with respect to adverse reactions, this biweekly paclitaxel-based approach showed a more favorable toxicity profile as compared with weekly or 3-weekly paclitaxel-based regimens [27–30, 33, 34]. There was no grade 4 toxicity or treatment-related death in this study. The most common adverse reaction was grade 3 gastrointestinal toxicity such as anorexia, nausea/vomiting, and stomatitis, which were reported in 10, 10, and 3.3% of patients, respectively. Grade 3 hematological toxicity was observed in 10% of the cases (anemia, 6.7%; leucopenia, 3.3%) with no severe treatment-related morbidity such as febrile neutropenia.

The benefit-to-risk ratio and the sequence of chemotherapy regimens might be very important issues in the treatment of advanced gastric cancer. Several chemotherapy regimens have been introduced; nevertheless, their survival advantage appears to be marginal and significant treatment-related toxicities are usually inevitable [37, 38]. In addition, there is no consensus on a strategy for the sequential use of chemotherapy for advanced gastric cancer, e.g., whether to use strong chemotherapy regimens for the first- line setting or save aggressive regimens for the second- or third-line setting. Although there is no rule, we favor the following individualized approach: for fit patients, it seems reasonable to use more aggressive regimens to obtain longer survival, whereas for unfit patients who are elderly or have poor performance status, it might be better to use drugs without severe toxic effects to achieve palliative goals. From this perspective, the biweekly paclitaxel regimen with infusional 5-fluorouracil and leucovorin used in this study is an attractive option, especially in patients with relatively poor performance status.

In conclusion, the combination of biweekly paclitaxel and infusional 5-fluorouracil and leucovorin appears to be an active chemotherapy regimen with excellent tolerability, suggesting its use as an alternative treatment for patients with advanced gastric cancer, especially in elderly patients or those in poor condition. Although modest effects were shown, further trials are needed to determine the optimal paclitaxel dose and combination schedule to improve treatment outcome.

References

1. Roder DM (2002) The epidemiology of gastric cancer. Gastric Cancer 5(Suppl 1):5–11
2. Bae JM, Won YJ, Jung KW, Park JG (2002) Annual report of the Korea Central Cancer Registry Program 2000: based on registered data from 131 hospitals. Cancer Res Treat 34:77–83
3. Pisani P, Parkin DM, Bray F, Ferlay J (1999) Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 83:18–29
4. Verdecchia A, Mariotto A, Gatta G, Bustamante-Teixeira MT, Ajiki W (2003) Comparison of stomach cancer incidence and survival in four continents. Eur J Cancer 39:1603–1609
5. Wöhrer SS, Raderer M, Hejna M (2004) Palliative chemotherapy for advanced gastric cancer. Ann Oncol 15:1585–1595
6. Schöffski P (2002) New drugs for treatment of gastric cancer. Ann Oncol 13(Suppl 4):13–22
7. Wils J (1998) Treatment of gastric cancer. Curr Opin Oncol 10:357–361
8. Vanhoefer U, Wilke H, Weh HJ, Clemens M, Harstrick A, Stahl M, Hossfeld DK, Seeber S (1994) Weekly high-dose 5-fluorouracil and folinic acid as salvage treatment in advanced gastric cancer. Ann Oncol 5:850–851
9. Jäger E, Bernhard H, Klein O, Wächter B, Theiss F, Dippold W, Meyer zum Büschenfelde KH, Knuth A (1995) Combination 5-fluorouracil (FU), folinic acid (FA), and alpha-interferon 2B in advanced gastric cancer: results of a phase II trial. Ann Oncol 6:153–156
10. Hsu CH, Yeh KH, Chen LT, Liu JM, Jan CM, Lin JT, Chen YC, Cheng AL (1997) Weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin in the treatment of advanced gastric cancers: an effective and low-toxic regimen for patients with poor general condition. Oncology 54:275–280
11. Parness J, Horwitz SB (1981) Taxol binds to polymerized tubulin in vitro. J Cell Biol 91:479–487
12. Chang YF, Li LL, Wu CW, Liu TY, Lui WY, P'eng FK, Chi CW (1996) Paclitaxel-induced apoptosis in human gastric carcinoma cell lines. Cancer 77:14–18
13. Ohtsu A, Boku N, Tamura F, Muro K, Shimada Y, Saigenji K, Akazawa S, Kitajima M, Kanamaru R, Taguchi T (1998) An early phase II study of a 3-hour infusion of paclitaxel for advanced gastric cancer. Am J Clin Oncol 21:416–419
14. Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, Miyata Y, Taguchi T (2001) Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol 12:1133–1137
15. Cascinu S, Ficarelli R, Safi MA, Graziano F, Catalano G, Cellerino R (1997) A phase I study of paclitaxel and 5-fluorouracil in advanced gastric cancer. Eur J Cancer 33:1699–1702
16. Grem JL, Nguyen D, Monahan BP, Kao V, Geoffroy FJ (1999) Sequence-dependent antagonism between fluorouracil and paclitaxel in human breast cancer cells. Biochem Pharmacol 58:477–486
17. Kim NK, Park YS, Heo DS, Suh C, Kim SY, Park KC, Kang YK, Shin DB, Kim HT, Kim HJ, Kang WK, Suh CI, Bang YJ (1993) 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 71:3813–3818
18. Ychou M, Astre C, Rouanet P, Fabre JM, Saint-Aubert B, Domergue J, Ribard D, Ciurana AJ, Janbon C, Pujol H (1996) A phase II study of 5-fluorouracil, leucovorin and cisplatin (FLP) for metastatic gastric cancer. Eur J Cancer 32A:1933–1937
19. MacDonald JS, Schein PS, Woolley PV, Smythe T, Ueno W, Hoth D, Smith F, Boiron M, Gisselbrecht C, Brunet R, Lagarde C (1980) 5-Fluorouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. Ann Intern Med 93:533–536
20. Wils JA, Klein HO, Wagener DJ, Bleiberg H, Reis H, Korsten F, Conroy T, Fickers M, Leyvraz S, Buyse M (1991) Sequential high-dose methotrexate and fluorouracil combined with doxorubicin—a step ahead in the treatment of advanced gastric cancer: a trial of

the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. J Clin Oncol 9:827–831
21. Zaniboni A, Barni S, Labianca R, Marini G, Pancera G, Giaccon G, Piazza E, Signaroldi A, Legnani W, Luporini G (1995) Epirubicin, cisplatin, and continuous infusion 5-fluorouracil is an active and safe regimen for patients with advanced gastric cancer. An Italian Group for the Study of Digestive Tract Cancer (GISCAD) report. Cancer 76:1694–1699
22. Wilke H, Preusser P, Fink U, Achterrath W, Lenaz L, Stahl M, Schober C, Link H, Meyer HJ, Lucke B (1990) High dose folinic acid/etoposide/5-fluorouracil in advanced gastric cancer—a phase II study in elderly patients or patients with cardiac risk. Invest New Drugs 8:65–70
23. Preusser P, Wilke H, Achterrath W, Fink U, Lenaz L, Heinicke A, Meyer J, Meyer HJ, Buente H (1989) Phase II study with the combination etoposide, doxorubicin, and cisplatin in advanced measurable gastric cancer. J Clin Oncol 7:1310–1317
24. Chao Y, Yeh KH, Chang CJ, Chen LT, Chao TY, Wu MF, Chang CS, Chang JY, Chung CY, Kao WY, Hsieh RK, Cheng AL (2004) Phase II study of weekly oxaliplatin and 24-h infusion of high-dose 5-fluorouracil and folinic acid in the treatment of advanced gastric cancer. Br J Cancer 91:453–458
25. Louvet C, Andre T, Tigaud JM, Gamelin E, Douillard JY, Brunet R, Francois E, Jacob JH, Levoir D, Taamma A, Rougier P, Cvitkovic E, de Gramont A (2002) Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 20:4543–4548
26. Ajani JA, Fairweather J, Dumas P, Patt YZ, Pazdur R, Mansfield PF (1998) Phase II study of Taxol in patients with advanced gastric carcinoma. Cancer J Sci Am 4:269–274
27. Kim JG, Sohn SK, Song HS, Kwon KY, Do YR, Lee KH, Hyun MS, Ryoo HM, Bae SH, Park KU, Baek JH, Lee WS, Chung JS, Cho GJ, Sohn CH, Jang JS, Chung HY, Yu W (2007) Multicenter phase II study of weekly paclitaxel plus cisplatin combination chemotherapy in patients with advanced gastric cancer. Cancer Chemother Pharmacol 60:863–869
28. Bokemeyer C, Lampe CS, Clemens MR, Hartmann JT, Quietzsch D, Forkmann L, Kollmannsberger C, Kanz L (1997) A phase II trial of paclitaxel and weekly 24 h infusion of 5-fluorouracil/folinic acid in patients with advanced gastric cancer. Anticancer Drugs 8:396–399
29. Kollmannsberger C, Quietzsch D, Haag C, Lingenfelser T, Schroeder M, Hartmann JT, Baronius W, Hempel V, Clemens M, Kanz L, Bokemeyer C (2000) A phase II study of paclitaxel, weekly, 24-hour continuous infusion 5-fluorouracil, folinic acid and cisplatin in patients with advanced gastric cancer. Br J Cancer 83:458–462
30. Gadgeel SM, Shields AF, Heilbrun LK, Labadidi S, Zalupski M, Chaplen R, Philip PA (2003) Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. Am J Clin Oncol 26:37–41
31. Murad AM, Petroianu A, Guimaraes RC, Aragao BC, Cabral LO, Scalabrini-Neto AO (1999) Phase II trial of the combination of paclitaxel and 5-fluorouracil in the treatment of advanced gastric cancer: a novel, safe, and effective regimen. Am J Clin Oncol 22:580–586
32. Honecker F, Kollmannsberger C, Quietzsch D, Haag C, Schroeder M, Spott C, Hartmann JT, Baronius W, Hempel V, Kanz L, Bokemeyer C (2002) Phase II study of weekly paclitaxel plus 24-h continuous infusion 5-fluorouracil, folinic acid and 3-weekly cisplatin for the treatment of patients with advanced gastric cancer. Anticancer Drugs 13:497–503
33. Kim YH, Shin SW, Kim BS, Kim JH, Kim JG, Mok YJ, Kim CS, Rhyu HS, Hyun JH, Kim JS (1999) Paclitaxel, 5-fluorouracil, and cisplatin combination chemotherapy for the treatment of advanced gastric carcinoma. Cancer 85:295–301
34. Chao Y, Li CP, Chao TY, Su WC, Hsieh RK, Wu MF, Yeh KH, Kao WY, Chen LT, Cheng AL (2006) An open, multi-centre, phase II clinical trial to evaluate the efficacy and safety of paclitaxel, UFT, and leucovorin in patients with advanced gastric cancer. Br J Cancer 95:159–163
35. Zhou NN, Zhou ZM, Liu MZ, Li YH, Xu RH, Teng XY, Xiang XJ, Tian WH, Liu DG, Hu PL, Zhang B, Qiu HJ, Qian SY, He YJ (2003) Preliminary report of semimonthly 5-fluorouracil/leucovorin combined with paclitaxel in treatment of advanced gastric cancer (AGC). Ai Zheng 22:867–869
36. Feng JF, Lu JW, Sun XF (2004) Biweekly regimen of high dose of leucovorin, 5-fluorouracil, and paclitaxel for patients with advanced gastric cancer. Ai Zheng 23:1704–1706
37. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE (2006) Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 24:2903–2909
38. Pinto C, Di Fabio F, Siena S, Cascinu S, Rojas Llimpe FL, Ceccarelli C, Mutri V, Giannetta L, Giaquinta S, Funaioli C, Berardi R, Longobardi C, Piana E, Martoni AA (2007) Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). Ann Oncol 18:510–517