World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i8.1082

World J Gastroenterol 2011 February 28; 17(8): 1082-1087
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Paclitaxel based *vs* oxaliplatin based regimens for advanced gastric cancer

Xiao-Dong Li, Hua Shen, Jing-Ting Jiang, Han-Ze Zhang, Xiao Zheng, Yong-Qian Shu, Chang-Ping Wu

Xiao-Dong Li, Jing-Ting Jiang, Xiao Zheng, Chang-Ping Wu, Department of Oncology, the Third Affiliated Hospital of Soochow University, Changzhou 213003, Jiangsu Province, China
Hua Shen, Yong-Qian Shu, Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China
Han-Ze Zhang, Department of Epidemiology and Biostatistics, Nanjing Medical University, Nanjing 210029, Jiangsu Province, China
Author contributions: Wu CP designed the research; Li XD and Shen H collected the data; Jiang JT, Zhang HZ, Zheng X and Shu YQ analyzed the data; Li XD and Jiang JT wrote the paper.
Supported by The National Natural Science Foundation of China, No. 30872176, 30950022 and 30972703; and Grants from Jiangsu Province of China, No. K200403, Department of Public Health and Department of Science and Technology (BS2005616)
Correspondence to: Chang-Ping Wu, MD, Professor, Chief, Department of Oncology, the Third Affiliated Hospital of Soochow University, Changzhou 213003, Jiangsu Province, China. wcpjjt@163.com
Telephone: +86-519-68870978 Fax: +86-519-68870978
Received: October 9, 2010 Revised: November 30, 2010
Accepted: December 7, 2010
Published online: February 28, 2011

Abstract

AIM: To compare the efficacy and safety of paclitaxel combined with fluorouracil plus cisplatin (PCF), and oxaliplatin combined with fluorouracil plus leucovorin (FOLFOX-4) regimens for advanced gastric cancer (AGC).

METHODS: Ninety-four patients with AGC were randomly assigned to receive paclitaxel (50 mg/m^2 iv) on days 1, 8 and 15, cisplatin (20 mg/m^2 iv) and fluorouracil (750 mg/m^2 iv) on days 1-5, or oxaliplatin (85 mg/m^2 iv) and leucovorin (200 mg/m^2 iv) on day 1, followed by bolus fluorouracil (400 mg/m^2 iv) and fluorouracil (600 mg/m^2 iv) on days 1 and 2. The primary end point was the 1-year survival time.

RESULTS: The overall response rate (ORR) of the patients was 48.0% and 45.5% to PCF and FOLFOX-4, respectively. The disease control rate (DCR) of PCF and FOLFOX-4 was 82.0% and 81.8%, respectively. The median survival times (MSTs) of the patients were 10.8 and 9.9 mo, respectively, after treatment with PCF and FOLFOX-4. The 1-year survival rate of the patients was 36.0% and 34.1%, respectively, after treatment with PCF and FOLFOX-4. No significant difference was observed in ORR, DCR, MST or 1-year survival rate between the two groups. The most common adverse events were anemia, nausea and vomiting, and grade 3/4 alopecia in PCF treatment group, and anemia, grade 1/2 neurotoxic effect and grade 3/4 neutropenia in FOLFOX-4 treatment group.

CONCLUSION: Patients with AGC have a similar response rate to PCF and FOLFOX-4 regimens with a similar survival rate. The PCF and FOLFOX-4 regimens are efficacious and tolerable as a promising therapy for AGC.

Key words: Paclitaxel; Oxaliplatin; Advanced gastric cancer

Peer reviewer: Georgina Que, MD, Department of Surgery, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, United States

Li XD, Shen H, Jiang JT, Zhang HZ, Zheng X, Shu YQ, Wu CP. Paclitaxel based *vs* oxaliplatin based regimens for advanced gastric cancer. *World J Gastroenterol* 2011; 17(8): 1082-1087 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i8/1082.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i8.1082

INTRODUCTION

Gastric cancer is the second leading cause of cancer-relat-

ed death worldwide, with the highest incidence in Eastern Asian and European countries[1]. The incidence of gastric cancer in Jiangsu Province of China is particularly high, and the death rate is much higher than the national average[2]. Unfortunately, most patients with advanced gastric cancer (AGC) have a miserable outcome. Even after curative gastrectomy, 60% of AGC patients develop local recurrences or distant metastasis[3-5].

Although the efficacy of palliative chemotherapy is now widely accepted[6-8], no chemotherapeutic regimen has been established as the consensus standard treatment for AGC. Among various chemotherapy regimens, paclitaxel combined with fluorouracil plus cisplatin (PCF) and oxaliplatin combined with fluorouracil plus leucovorin (FOLFOX-4) regimens are the two commonly used modalities.

It has been demonstrated that paclitaxel, an anticancer agent which binds to microtubules and induces hyperstabilization leading to cell cycle arrest and apoptosis[9,10], has a promising efficacy against gastric cancer. The response rate of gastric cancer patients to it is about 20%-25%, and the median response time of gastric cancer patients is about 7 mo after treatment with paclitaxel[11-13]. It was reported that the response rate of patients with gastric cancer to PCF regimen is 33%[14-17].

Oxaliplatin, a third-generation diaminocyclohexane platinum compound that has a wide range of antitumor activities, appears to have a better safety profile than cisplatin in terms of nausea, vomiting, nephrotoxicity, and ototoxicity[18,19]. The response rate of AGC patients to FOLFOX-4 regimen is 38%-43% and FOLFOX-4 regimen shows a manageable toxicity profile as the first-line treatment modality for AGC[20-24].

As is commonly known, there is only one best regimen at one time. No study is available comparing the efficacy and safety of PCF and FOLFOX-4 regimens. Therefore, we designed the present study to observe the therapeutic indexes of the two regimens for AGC.

MATERIALS AND METHODS

Patients

The inclusion criteria for AGC patients were (1) pathologically proved locally advanced (non-resectable) or metastatic gastric cancer; (2) age between 20 and 75 years; (3) measurable or assessable lesions by imaging studies according to the RECIST guidelines[25]; (4) no prior chemotherapy except for postoperative adjuvant chemotherapy for more than 12 mo before entry into the study; (5) Eastern Cooperative Oncology Group (ECOG) performance status 0-2; (6) adequate bone marrow functions (hemoglobin level $\geqslant$ 90 g/L, white blood cell count of 4-10 $\times$ 10^9/L, neutrophil count $\geqslant$ 2 $\times$ 10^9/L, and platelet count $\geqslant$ 100 $\times$ 10^9/L), hepatic function (total bilirubin $\leqslant$ 1.5 $\times$ the institutional upper limit of normal value, aspartate aminotransferase/alanine aminotransferase $\leqslant$ 2.5 $\times$ the institutional upper limit of normal value, and alkaline phosphatase $\leqslant$ 2.5 $\times$ the institutional upper limit of normal value), renal function (serum creatinine level $\leqslant$ 1.5 mg/dL and creatinine clearance $\geqslant$ 50 mL/min); and (7) estimated life expectancy of at least 3 mo and no other malignancies.

The exclusion criteria for patients included (1) preexisting peripheral toxicity $\geqslant$ grade 2 of the National Cancer Institute Common Toxicity Criteria (NCI-CTC, Version 3.0); (2) pregnant, and breastfeeding women or women of child-bearing potential without adequate contraception; (3) concurrent or prior malignancy; (4) central nervous system metastases; (5) active infection; (6) other uncontrolled underlying medical conditions that would impair the ability of the patients to receive the planned treatment; (7) inadequate calorie and fluid intake; and (8) concurrent treatment that interfered with the study evaluation.

The study, approved by the ethics committees of all participating medical institutions, was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients gave their written informed consent before enrollment.

Treatment methods

The patients were divided into PCF group and FOLFOX-4 group. Patients in the PCF group received paclitaxel (50 mg/m^2 iv) for 3 h on days 1, 8 and 15, cisplatin (20 mg/m^2 iv) for 2 h on days 1-5, fluorouracil (750 mg/m^2 iv) for 24 h for 5 d. The treatment was repeated every 28 d for 6 cycles. Patients in the FOLFOX-4 group received oxaliplatin (85 mg/m^2 iv) and leucovorin (200 mg/m^2 iv) for 2 h on day 1, bolus fluorouracil (400 mg/m^2 iv) and fluorouracil (600 mg/m^2 iv) for 22 h on days 1 and 2. The treatment was repeated every 14 d for 12 cycles.

The dose was modified based on the hematologic parameters and the degree of non-hematologic toxicities. Physical examination, chest X-ray, complete blood test and biochemical tests were performed before each chemotherapy cycle. The toxicity was graded based on the NCI-CTC (Version 3.0).

Dose modification

The dose was modified for the PCF group as follows: (1) If the hepatotoxicity was grade 2, the dose of paclitaxel for the following treatment was reduced to 40 mg/m^2 on days 1, 8 and 15. If the hepatotoxicity was grade 3/4, the study was discontinued; (2) If the bone marrow suppression was grade 4, the dose of paclitaxel for the following treatment was reduced to 40 mg/m^2 on days 1, 8 and 15. If the bone marrow suppression was grade 4, the study was discontinued; (3) If the mucositis was grade 3/4, fluorouracil was administered from the next cycle for 3 d; and (4) If the creatinine clearance rate was 30-50 mL/min due to the nephrotoxicity, the dose of cisplatin was reduced by 50%. If the creatinine clearance rate was lower than 30 mL/min, the study was discontinued.

The dose was modified for the FOLFOX-4 group as

follows: (1) If the neurotoxic effect was grade 1/2, the dose of oxaliplatin was reduced by 25%. If the neurotoxic effect was grade 3/4 or persistent, the oxaliplatin was omitted from the regimen until the neurotoxic effect was resolved to grade 1 or better; (2) If the mucositis was grade 3/4, fluorouracil was administered from the next cycle for 3 d; and (3) If grade 3/4 diarrhea, stomatitis or dermatitis occurred, the dose of fluorouracil was reduced by 25%.

Evaluation

The parameters of 12-lead electrocardiogram, computed tomography (CT) scan, and levels of tumor markers (CA19-9, CA72-4, CA24-2 and carcinoembryonic antigen) were obtained from the patients within 7 d after enrollment. Hematology tests, biochemistry tests, and assessment of symptoms and signs were carried out for the patients within 3 d before enrollment and every week during the study period. CT scans were carried out and levels of tumor markers were measured before each cycle. According to the RECIST guidelines[17], responses concluded complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). To confirm the PR or CR, the levels of tumor markers were measured no less than 4 wk after the objective response was obtained. Responses were assessed by the independent review committee. The overall response rate (ORR) was defined as the sum of CR and PR rates. The disease control rate (DCR) was defined as the sum of CR, PR and SD rates. Toxic effects were evaluated according to the NCI-CTC (Version 3.0). The overall survival time (OST) was defined as the period from the date of treatment to the death of patients. The median survival time (MST) was defined as the half of OST.

Statistical analysis

Statistical analysis was performed with the SPSS software (Version 17.0, SPSS). Chi-square test was used to compare the categorical data. KaplanMeier method was used to calculate the OST. Logrank test was used to compare the OST. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of patients

From January 2003 to December 2007, 94 patients were enrolled in this study. The baseline clinical characteristics of the patients were compared between the two groups (Table 1). No significant difference was observed in any clinical characteristics between the two groups.

Objective response

All the patients were evaluated for their response to PCF and FOLFOX-4 regimens and no patient was excluded from the efficacy analysis because of severe side effects.

Of the patients in PCF group, 1 achieved a CR and 23 a PR, 17 had SD, and 9 PD, with an ORR of 48%. The response rate of patients who received prior chemotherapy to PCF was 52.6% (20/38) and 33.3% (4/12), respectively, with a DCR of 82.0%.

Of the patients in FOLFOX-4 group, 1 achieved a CR and 19 a PR, and 16 had SD and 8 PD, with an ORR of 45.5%. The response rate of patients who received prior chemotherapy to FOLFOX-4 was 54.8% (17/31) and 23.1% (3/13), respectively, with a DCR of 81.8%. No significance was observed in ORR and DCR between the two groups.

Table 1 Baseline characteristics of patients enrolled in this study (n = 73)

Characteristics	Patients (%)		P
	PCF (n = 50)	FOLFOX-4 (n = 44)	
Gender			
Female	18	13	0.520
Male	32	31	
Age (yr)			
Median	59	58	0.876
Range	20-74	20-75	
Histologic type			
Adenocarcinoma	34	36	0.158
Adenosquamous carcinoma	3	1	
Signet ring cell carcinoma	5	3	
Mucinous carcinoma	7	3	
Neuroendocrine carcinoma	1	1	
No. of metastatic lesion			
0-1	24	21	1
⩾ 2	26	23	
Stage			
Ⅲb	22	17	0.677
Ⅳ	28	27	
Prior adjuvant chemotherapy			
No	38	31	0.642
Yes	12	13	

PCF: Paclitaxel combined with fluorouracil plus cisplatin; FOLFOX-4: Oxaliplatin combined with fluorouracil plus leucovorin.

Survival analysis

The MST and the 1-year survival rate of patients in the PCF group was 10.8 mo (95% CI: 8.9-12.7 mo) and 36.0%, respectively.

The MST and the 1-year survival rate of patients in the FOLFOX-4 group was 9.9 mo (95% CI: 8.3-11.4 mo) and 34.1%, respectively.

No significant difference was found in MST and survival rate between the two groups (Figure 1).

Profile of safety and adverse events

No patient was excluded from the efficacy analysis because of severe side effects. Grade 3/4 neutropenia occurred in 8% and 10% of patients in the PCF and FOLFOX-4 groups, respectively. Anemia occurred in 60% and 57% of patients in the PCF and FOLFOX-4 groups, respectively. Nausea and vomiting occurred in 12.0% and 9% of patients in the PCF and FOLFOX-4 groups, respectively.

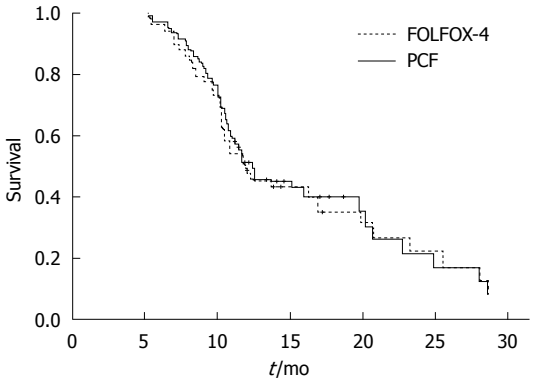

Figure 1 Overall survival curves for patients in PCF and FOLFOX-4 groups. PCF: Paclitaxel combined with fluorouracil plus cisplatin; FOLFOX-4: Oxaliplatin combined with fluorouracil plus leucovorin.

Grade 3/4 alopecia occurred in 10.0% and 0% of patients in the PCF group and FOLFOX-4 group, respectively ($P < 0.05$). Grade 1/2 neurotoxic effect was observed in 6% and 17% of patients in the PCF group and FOLFOX-4 group, respectively ($P < 0.05$).

Diarrhea, hepatic or renal toxicities and oral mucosa ulcer were relatively infrequent and slight.

DISCUSSION

In China, gastric cancer patients are usually diagnosed at a relative advanced stage with metastasis to other organs[26]. Although a number of treatment modalities for gastric cancer such as surgical resection combined with chemotherapy are available[27,28], no current regimen can be considered a standard therapy for AGC, thus new therapeutic strategies are required to achieve a better clinical efficacy with an acceptable toxicity profile. PCF and FOLFOX-4 regimens are commonly used as the first-line therapy for AGC. The efficacies of the two regimens against AGC are similar with different adverse events.

Taxane is one of the three milestones of anti-cancer drugs, used in the 1990s. It was reported that the ORR of AGC patients to PCF is 34%-52%[13]. The survival time of most AGC patients does not exceed 12 mo after PCF therapy with taxane or 5-FU plus cisplatin[11,12]. Kim *et al*[14] reported that the MST of AGC patients is 13.2 mo. The results of this study are consistent with the reported findings[11,12]. Overall, the efficacy of PCF against AGC is stable.

Oxalipaltin has been used in treatment of advanced colorectal carcinoma. It has been shown that the response rate of patients with advanced colorectal carcinoma to oxaliplatin in combination with fluorouracil is 36%-58%[29-31]. Vita *et al*[32] revealed that the ORR of patients with advanced colorectal carcinoma to oxaliplatin is 38% with a TTP of 7.1 mo and an OST of 11.2 mo. The results of the current study indicate that a biweekly FOLFOX-4 regimen can significantly improve the symptoms of AGC patients. The decreased ORR observed in our study might be related to the selected gastric cancer patients at ⅢB or Ⅳ stage. Considering the smaller sample size and the modified doses in the present study, further study is warranted to confirm the results.

It was reported that the toxic rate of FOLFOX-4 regimen for grade 3/4 neutropenia, and nausea and vomiting is 7.6%-34% and 4%-18.1%, respectively[13], which is consistent with our results. In the present study, the neurotoxic rate of FOLFOX-4 regimen for diarrhea and oral mucosa ulcer was low, which might be due to the low PS score. The reported neurotoxic rate of PCF regimen for grade 3/4 neutropenia is 22%-86%[12,33], which is also consistent with our results. Alopecia occurred more frequently in PCF group than in FOLFOX-4 group, and vice versa. Overall, these regimens may not only prolong the survival time but also for improve the life quality of gastric cancer patients.

In summary, both PCF and FOLFOX-4 regimens can be used in treatment of AGC. Further study is warranted to confirm the results of this study.

COMMENTS

Background

Gastric cancer is the second most common cause of cancer-related death globally. Its incidence is the highest in Eastern Asian and European countries. Unfortunately, most gastric cancer patients are at the advanced stage when they are diagnosed. The outcome of patients with advanced gastric cancer (AGC) is poor. Chemotherapy is often used for AGC and its efficacy is now widely accepted. However, no standard combination of chemical drugs has been established. Among the different combinations, paclitaxel combined with fluorouracil plus cisplatin (PCF) and oxaliplatin combined with fluorouracil plus leucovorin (FOLFOX-4) regimens are the two commonly used modalities. There is only one best regimen at one time. No study comparing the efficacy and safety of PCF and FOLFOX-4 regimens is available at present. Therefore, we designed the present phase-2 study to observe the therapeutic indexes of the two regimens for AGC.

Research frontiers

No current regimen can be considered as a standard therapy for AGC. PCF and FOLFOX-4 regimens are the commonly used first-line therapy for AGC. The overall survival rate (ORR) of AGC patients is 34%-52% after PCF therapy. The survival time of most AGC patients after PCF therapy with taxane, or 5-FU plus cisplatin does not exceed 12 mo. It was reported that the response rate of AGC patients to FOLXOF-4 regimen is 36%-58%. Both PCF and FOLFOX-4 regimens can be used in treatment of AGC.

Innovations and breakthroughs

No study comparing the efficacy and safety of PCF and FOLFOX-4 regimens. Therefore, we designed the present phase Ⅱ study to observe the therapeutic indexes of the two regimens for AGC. The results of this study show that the two regimens are benefit not only for survival but also for quality of life patients after resection of colorectal cancer.

Applications

PCF regimen can be used for those who need to do fine jobs, and FOLFOX-4 regimen can be used for those who care more about their appearance. The current study may help patients to take more consideration about various demands in daily life.

Peer review

The present study provides important data about PCF and FOLFOX-4 regimens for gastric cancer and the article is well written.

REFERENCES

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

2 **Shen X**, Zhang J, Yan Y, Yang Y, Fu G, Pu Y. Analysis and estimates of the attributable risk for environmental and genetic risk factors in gastric cancer in a Chinese population. *J Toxicol Environ Health A* 2009; **72**: 759-766
3 **Wilke H**, Preusser P, Fink U, Achterrath W, Mayer HJ, Stahl M, Lenaz L, Meyer J, Siewert JR, Gerlings H. New developments in the treatment of gastric carcinoma. *Cancer Treat Res* 1991; **55**: 363-373
4 **Rivera F**, Vega-Villegas ME, López-Brea MF. Chemotherapy of advanced gastric cancer. *Cancer Treat Rev* 2007; **33**: 315-324
5 **Macdonald JS**. Treatment of localized gastric cancer. *Semin Oncol* 2004; **31**: 566-573
6 **Murad AM**, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993; **72**: 37-41
7 **Pyrhönen S**, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995; **71**: 587-591
8 **Glimelius B**, Ekström K, Hoffman K, Graf W, Sjödén PO, Haglund U, Svensson C, Enander LK, Linné T, Sellström H, Heuman R. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997; **8**: 163-168
9 **Schiff PB**, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by taxol. *Nature* 1979; **277**: 665-667
10 **Ganansia-Leymarie V**, Bischoff P, Bergerat JP, Holl V. Signal transduction pathways of taxanes-induced apoptosis. *Curr Med Chem Anticancer Agents* 2003; **3**: 291-306
11 **Ajani JA**, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Awad L, Van Cutsem E. Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: the V-325 Study Group. *J Clin Oncol* 2007; **25**: 3210-3216
12 **Van Cutsem E**, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991-4997
13 **Im CK**, Jeung HC, Rha SY, Yoo NC, Noh SH, Roh JK, Chung HC. A phase II study of paclitaxel combined with infusional 5-fluorouracil and low-dose leucovorin for advanced gastric cancer. *Cancer Chemother Pharmacol* 2008; **61**: 315-321
14 **Kim YH**, Shin SW, Kim BS, Kim JH, Kim JG, Mok YJ, Kim CS, Rhyu HS, Hyun JH, Kim JS. Paclitaxel, 5-fluorouracil, and cisplatin combination chemotherapy for the treatment of advanced gastric carcinoma. *Cancer* 1999; **85**: 295-301
15 **Murad AM**, Petroianu A, Guimaraes RC, Aragao BC, Cabral LO, Scalabrini-Neto AO. 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* 1999; **22**: 580-586
16 **Roth AD**, Maibach R, Martinelli G, Fazio N, Aapro MS, Pagani O, Morant R, Borner MM, Herrmann R, Honegger H, Cavalli F, Alberto P, Castiglione M, Goldhirsch A. Docetaxel (Taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology (EIO). *Ann Oncol* 2000; **11**: 301-306
17 **Shin SJ**, Chun SH, Kim KO, Kim MK, Lee KH, Hyun MS, Bae SH, Ryoo HM, Do YR, Kwon KY, Song HS. The efficacy of paclitaxel and cisplatin combination chemotherapy for the treatment of metastatic or recurrent gastric cancer: a multicenter phase II study. *Korean J Intern Med* 2005; **20**: 135-140
18 **Di Francesco AM**, Ruggiero A, Riccardi R. Cellular and molecular aspects of drugs of the future: oxaliplatin. *Cell Mol Life Sci* 2002; **59**: 1914-1927
19 **Eriguchi M**, Nonaka Y, Yanagie H, Yoshizaki I, Takeda Y, Sekiguchi M. A molecular biological study of anti-tumor mechanisms of an anti-cancer agent Oxaliplatin against established human gastric cancer cell lines. *Biomed Pharmacother* 2003; **57**: 412-415
20 **Louvet C**, André T, Tigaud JM, Gamelin E, Douillard JY, Brunet R, François E, Jacob JH, Levoir D, Taamma A, Rougier P, Cvitkovic E, de Gramont A. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. *J Clin Oncol* 2002; **20**: 4543-4548
21 **Al-Batran SE**, Atmaca A, Hegewisch-Becker S, Jaeger D, Hahnfeld S, Rummel MJ, Seipelt G, Rost A, Orth J, Knuth A, Jaeger E. Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. *J Clin Oncol* 2004; **22**: 658-663
22 **Chao Y**, Yeh KH, Chang CJ, Chen LT, Chao TY, Wu MF, Chang CS, Chang JY, Chung CY, Kao WY, Hsieh RK, Cheng AL. 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* 2004; **91**: 453-458
23 **Lordick F**, Lorenzen S, Stollfuss J, Vehling-Kaiser U, Kullmann F, Hentrich M, Zumschlinge R, Dietzfelbinger H, Thoedtmann J, Hennig M, Seroneit T, Bredenkamp R, Duyster J, Peschel C. Phase II study of weekly oxaliplatin plus infusional fluorouracil and folinic acid (FUFOX regimen) as first-line treatment in metastatic gastric cancer. *Br J Cancer* 2005; **93**: 190-194
24 **Cavanna L**, Artioli F, Codignola C, Lazzaro A, Rizzi A, Gamboni A, Rota L, Rodinò C, Boni F, Iop A, Zaniboni A. Oxaliplatin in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in patients with metastatic gastric cancer (MGC). *Am J Clin Oncol* 2006; **29**: 371-375
25 **Therasse P**, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205-216
26 **Chen L**, Tian H, Chen J, He ZG, Tao SF, Lokesh G, Peng SY. Surgical management of gastric stump cancer: a report of 37 cases. *J Zhejiang Univ Sci* B 2005; **6**: 38-42
27 **Kollmannsberger C**, Budach W, Stahl M, Schleucher N, Hehr T, Wilke H, Schleicher J, Vanhoefer U, Jehle EC, Oechsle K, Trarbach T, Boehlke I, Kanz L, Hartmann JT, Bokemeyer C. Adjuvant chemoradiation using 5-fluorouracil/folinic acid/cisplatin with or without paclitaxel and radiation in patients with completely resected high-risk gastric cancer: two cooperative phase II studies of the AIO/ARO/ACO. *Ann Oncol* 2005; **16**: 1326-1333
28 **Lin WL**, Li DG, Chen Q, Lu HM. Clinical and experimental study of oxaliplatin in treating human gastric carcinoma. *World J Gastroenterol* 2004; **10**: 2911-2915
29 **Lévi F**, Misset JL, Brienza S, Adam R, Metzger G, Itzakhi M, Caussanel JP, Kunstlinger F, Lecouturier S, Descorps-Declère A. A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid, and oxaliplatin using an ambulatory multichannel programmable pump. High antitumor effectiveness against metastatic colorectal cancer. *Cancer* 1992; **69**: 893-900
30 **Lévi FA**, Zidani R, Vannetzel JM, Perpoint B, Focan C, Faggiuolo R, Chollet P, Garufi C, Itzhaki M, Dogliotti L. Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. *J Natl Cancer Inst* 1994; **86**: 1608-1617
31 **de Gramont A**, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud

F, Wilson C, Morvan F, Bonetti A. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; **18**: 2938-2947

32 **De Vita F**, Orditura M, Matano E, Bianco R, Carlomagno C, Infusino S, Damiano V, Simeone E, Diadema MR, Lieto E, Castellano P, Pepe S, De Placido S, Galizia G, Di Martino N, Ciardiello F, Catalano G, Bianco AR. A phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and folinic acid (FOLFOX-4) as first-line treatment of advanced gastric cancer patients. *Br J Cancer* 2005; **92**: 1644-1649

33 **Lorenzen S**, Hentrich M, Haberl C, Heinemann V, Schuster T, Seroneit T, Roethling N, Peschel C, Lordick F. Split-dose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial. *Ann Oncol* 2007; **18**: 1673-1679

S- Editor Sun H **L- Editor** Wang XL **E- Editor** Zheng XM