RESEARCH ARTICLE

Phase II Study on Pemetrexed-based Chemotherapy in Treating Patients with Metastatic Gastric Cancer not Responding to Prior Palliative Chemotherapy

Guo-Li Wei[1,2&], Xin-En Huang[1&*], Jie-Ge Huo[2*], Xiao-Ning Wang[2], Jin-Hai Tang[3*]

Abstract

Purpose: This study was to determine the efficacy and safety of pemetrexed based chemotherapy in treating patients with metastatic gastric cancer who failed to respond to first and (or) second line chemotherapy. Patients and Methods: Metastatic gastric cancer patients who failed first and (or) second line chemotherapy, were enrolled. All patients were recruited from Jiangsu Cancer Hospital & Research Institute, and were treated with pemetrexed 500 mg/m^2 (intravenous; on day 1), and a platinum (or irinotecan) every 3 weeks until disease progression, or intolerable toxicity. Evaluation on efficacy was conducted after two cycles of chemotherapy using the Response Evaluation Criteria for Solid Tumors. Toxicity was recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Results: From Jun 2011 to May 2013, 23 patients were enrolled. All eligible 23 patients completed at least 2 cycles of chemotherapy with pemetrexed based chemotherapy, and were evaluable. Their median age was 55 years (range 40 to 78 years). Seventeen patients were male and 6 female. Three patients (13%) achieved partial response, five patients (22%) stable, 15 patients (65%) with disease progression, and none with complete response. Grade 2 neutrophil suppression occurred in 4.3%, grade 3 in 13% of patients, and no grade 4 was reported. Thrombocytopenia was encountered as follows: 4.3% grade 2, 4.3% grade 3 and 4.3% grade 4. Incidence of anemia was 34.8% in grade 2, 8.7% grade 3 and 0% grade 4. Only 4.3% of patients required packed red blood cell infusion. Elevated transaminase were 4.3% in grade 2 and 0% in grade 3 or 4. Other toxicity included oral mucositis. Conclusions: Pemetrexed based chemotherapy is mildly effective in treating patients with metastatic gastric cancer with tolerable toxicity.

Keywords: Metastatic gastric cancer - pemetrexed - phase II study

Asian Pacific J Cancer Prev, **14 (5)**, 2703-2706

Introduction

Gastric cancer remains one of the leading causes of cancer death worldwide (Parkin et al., 2002). Patients suffering from advanced gastric cancer (AGC) remain a therapeutic challenge for medical oncologists. Randomized trials proved that palliative chemotherapy brings survival benefits over best supportive care for metastatic gastric cancer (Wagner et al., 2010). Despite increasing evidence that appropriate management for fit patients is chemotherapy, no combination is considered as a standard of care. Active chemotherapeutic agents in first line chemotherapy for advanced gastric cancer include 5-fluorouracil, cisplatin, and anthracyclines (Ohtsu, 2008). New generation agents, including taxanes, ironotecan, oxaliplatin and pemetrexed are reported to be active in treating patients with gastric cancer (Pozzo et al., 2008). The response rate of above-mentioned single agent is around 10 to 25%, with significant toxicities. Therefore, it is urgent to develop effective regimens with acceptable toxicity profiles, and patient convenience, as well as improving quality of life for these patients (Ajani, 2005).

New multitargeted antifolate pemetrexed is suggested to have an important advantage compared with prolonged 5-FU schedules in that it is administered via a single short injection (Celio et al., 2009). Pemetrexed demonstrated activity in a variety of tumor types based on previous reports, including non-small cell lung cancer, malignant pleural mesothelioma, pancreas, colorectal, gastric, bladder, breast, head and neck cancers(Martin, 2006; Bajetta et al., 2003). Pemetrexed is reported to be more active than 5-FU against several human gastric cancer cell lines (Kim et al., 2005).

Thus we conduct this phase II trail to study the clinical efficacy and tolerability of pemetrexed in treating patients with metastatic gastric cancer who failed to respond to first and (or) second line chemotherapy.

*[1]Department of Chemotherapy, [3]Department of General Surgery, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, [2]Jiangsu Province Hospital on Integration of Chinese and Western Medicine, Nanjing, China [&]Equal contributors *For correspondence: huangxinen06@aliyun.com, zgzlwkzz@139.com, hjg16688@163.com*

Materials and Methods

Patient eligibility

Eligible patients should be histologically confirmed adenocarcinoma of the stomach or gastro-esophageal junction with clinical evidence of metastatic disease, and have received prior systemic chemotherapy or radiation therapy for gastric cancer. Other eligible criteria include: age≥18 years; adequate bone marrow (platelets≥100×10^9 cells/l, absolute neutrophil count≥1.5×10^9 cells/l), hepatic (total bilirubin ≤ 2×the upper limit of normal;aspartate transaminase ≤ 3×the upper limit of normal or ≤ 5× the upper limit of normal if metastatic disease was present in the liver) and calculated creatinine clearance, ≥ 45 ml/min, using the modified Cockcroft and Gault calculated creatinine clearance formula; a life expectancy of ≥ 3 months; sign an informed consent before chemotherapy. Complete patient histories, physical examinations, complete blood cell counts, chemistries (aspartate aminotransferase, total bilirubin, creatinine, albumin), calculated creatinine clearance were performed at baseline prior to each course of treatment. Complete blood cell count was repeated weekly. Radiological studies (roentgenograms,computed axial tomographic scans or magnetic resonance imaging) were performed at baseline and after every two cycles of therapy to assess tumor response. CR was defined as complete disappearance of all measurable disease. Partial response (PR) was defined as at least 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. Progression was defined as 50% increase or an increase of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) or appearance of any new lesion, or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). Stable disease (SD) was documented when there was persistence of disease without meeting the criteria for progression, PR or CR.

Treatment

Pemetrexed 500 mg/m^2 was given intravenously on day 1, premedication was conducted, and repeated every 3 weeks: 400 μg of folic acid was given orally daily and 1000 μg of vitamin B12 was given intramuscularly every 9 weeks starting 7 days prior to the first dose and until 3 weeks after the last dose of pemetrexed; 4.5 mg of dexamethasone was given orally every 12 h on the day before, day of and the day after pemetrexed. Antiemetics were given with chemotherapy on days 1. Colony-stimulating factors were not used prophylactically to prevent granulocytopenia. Treatment continued until disease progression, unacceptable toxicities. All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version2.0) (National Cancer Institute, 1998).

Research experience

We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Gong et al., 2012; Gu et al., 2012; Li et al., 2012; Yu et al., 2012; Zhan et al., 2012; Zhan et al., 2012; Deng et al., 2013; Huang et al., 2013; Liu et al., 2013; Liu et al., 2013; Lu et al., 2013; Wu et al., 2013; Yin et al., 2013; Yin et al., 2013).

Results

Patients

A total of 23 patients were enrolled from Jun 2011 to May 2013. All patients received at least one systemic chemotherapy. Twenty-one patients had adenocarcinoma of the stomach and two cases were diagnosed with adenocarcinoma of the gastro-esophageal junction. Fourteen patients received pemetrexed based combination therapy as second line, 6 as third, and 3 as 4th line chemotherapy. General characteristics of patients were listed in Table 1.

Efficacy

Nineteen patients completed at least 2 cycles of chemotherapy, and were evaluated according to study protocol. Overall, Three patients (13%) achieved PR, while five patients (22%) remained stable, no CR. RR was 13%, DCR 35%. Twenty patients received pemetrexed combined with other agents, and 3 patients were treated with pemetrexed alone (Table 2).

Table 1. General Characteristics of Patients (n=23)

Characteristic	Patients, n(%)
Age, years	
Median	55
Range	40-78
Sex	
Male	6 (27%)
Female	17 (73%)
ECOG performance status	
≤2	23 (100%)
>2	0
Number of organs involved	
1	15 (65%)
≥2	8 (35%)
Sites of metastases	
Lymph node	23 (100%)
Peritoneum	10 (43%)
Liver	5 (22%)
Lung	2 (9%)
Bone	1 (4%)

ECOG, Eastern Cooperative Oncology Group

Table 2. The Patients' Chemotherapy (n=23)

Chemotherapy	Patients, n(%)
PEM(500 mg/m^2)d1+CPT-11(150 mg/m^2) d1,8	8 (35%)
PEM (500 mg/m^2)d1+CBP (300 mg/m^2)d2	4 (17%)
PEM (500 mg/m^2)d1+DDP (60 mg/m^2)d1-5	3 (13%)
PEM (500 mg/m^2)d1+OXA (100 mg/m^2)d2	1 (4%)
PEM (500 mg/m^2)d1+lobaplatin(30 mg/m^2)d2	1 (4%)
PEM (500 mg/m^2)d1+EPI(60 mg/m^2) d1-2	3 (13%)
PEM (500 mg/m^2)d1	3 (13%)

Table 3. Common Grade 1 to 4 Toxicities[a]

Type	Grade 1 (%)	Grade2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	6 (26.1%)	1 (4.3%)	3 (13%)	0
Anemia	6 (26.1%)	8 (34.8%)	2 (8.7%)	0
Thrombocytopenia	1 (4.3%)	1 (4.3%)	0	1 (4.3%)
Elevated transaminase	2 (8.7%)	1 (4.3%)	0	0
Bilirubin	2 (8.7%)	2 (8.7%)	0	0
Creatinine	0	0	0	0

[a]Toxicity graded according to National Cancer Institute Common Toxicity Criteria

Toxicity

Without prophylactic colony-stimulating factors support, 4.3% of patients had absolute neutrophil count nadir values constituting grade 2 toxicity, 13% had grade 3 toxicity, no one had grade 4 toxicity. Anemia occurred with incidences of 34% in grade2, 8.7% in grade 3 and 0% in grade 4. Only 4.3% of patients required packed red blood cell transfusion. Thrombocytopenia was 4.3% in grade 2, 0% in grade 3 and 4.3% in grade 4. One patient (4.3%) required packed platelet transfusion. Bilirubin abnormal incidence was 8.7% in grad 2, 0% in grad 3 and 4. No Creatinine changed abnormally. Other toxicities include elevated transaminase, oral mucositis and skin rash. No neurological , renal and ototoxic adverse reaction were recorded (Table 3).

Discussion

Gastric cancer is the second most common cause of tumor-related death worldwide (Parkin et al., 2001). Fluorouracil (5-FU) remains the most widely used chemotherapeutic agent for patients with advanced gastric cancer, with a response rate of 20% (Karpeh et al., 2001). However, patients with metastatic gastric cancer are associated with poorer prognosis compared with those with locally advanced disease (Ross et al , 2002). At present, no standard therapy is established when patients failed to response to fluorouracil based chemotherapy. Pemetrexed is a recently developed antifolate agent with a favorable toxicity profile, and could be well tolerated in patients who were treated with third- or further-line treatment (Pozzo et al., 2008). Although activity of pemetrexed against breast, gastric, pancreatic and colorectal adenocarcinoma cell lines was reported (Adjei, 2004), only several phase I or II studies containing pemetrexed were conducted for patients with gastric cancer, with a response rate ranging from 21% to 36% (Celio et al., 2002; Bajetta1 et al., 2003; Kim, 2008; Celio et al., 2009; Chen, 2010). In this study, all patients were staged IV and failed after treatment with fluorouracil based chemotherapy. There are 12 (61%) patients received pemetrexed based combination therapy as second line, 6 (26%) patients as third line , and 3 (13%) patients as 4 lines. Overall, Three patients (13% , two as second line and one as third line) achieved PR, while five patients (22%) remained stable, progression of disease, with no completer emission, RR was 13%, DCR 35%. Toxicity of pemetrexed based combination therapy was mild and resulted in a low incidence of severe adverse events (< 5%). Main toxicity was myelosuppressionin in this trial. Three to 4 grade neutropenia, anemia and thrombocytopenia were 13%, 8.7% and 4.3% respectively. Leukocyte and platelet returned to normal level after treatment with colony-stimulating factor, interleukin 11 and recombinant human thrombopoietin.

In conclusion, our study provides a treatment option for patients with metastatic gastric cancer who failed after at least one chemotherapy. Pemetrexed based chemotherapy is mildly effective in this setting, with tolerable toxicities. However, we should get more evidence to know which is the best combination with pemetrexed before further phase III studies.

Acknowledgements

Dr. Xin-En Huang is supported in part by a grant from Jiangsu Provincial Administration of Traditional Chinese Medicine (LZ11091), and in part from a special research fund from Organization Department of Jiangsu Provincial Party Committee, Talent Work Leading Group of Jiangsu Province (333 High-level Personnel Training Project).

References

Adjei AA (2004). Pemetrexed (ALIMTA), a novel multitargeted antineoplastic agent. *Clin Cancer Res*, **10**, S4276-80.

Ajani JA (2005). Evolving chemotherapy for advanced gastric cancer. *Oncologist*, **10**, 49-58.

Bajetta E, Celio L, Buzzoni R, et al (2003). Phase II study of pemetrexed disodium (alimta) administered with oral folic acid in patients with advanced gastric cancer. *Ann Oncol*, **14**, 1543-8.

Celio L, Buzzoni R, Longarini R, et al (2002). Pemetrexed in gastric cancer: clinical experience and future perspectives. *Semin Oncol*, **29**, 63-8.

Celio L, Sternberg CN, Labianca R, et al (2009). Pemetrexed in combination with oxaliplatin as a first-line therapy for advanced gastric cancer: a multi-institutional phase II study. *Ann Oncol*, **20**, 1062-1067.

Chen JS, Chao Y, Bang YJ, et al (2010). A phase I/II and pharmacogenomic study of pemetrexed and cisplatin in patients with unresectable, advanced gastric carcinoma. *Anticancer Drugs*, **21**, 777-84.

Deng QQ, Huang XE, Ye LH, et al (2013). Phase II trial of Loubo® (Lobaplatin) and pemetrexed for patients with metastatic breast cancer not responding to anthracycline or taxanes. *Asian Pac J Cancer Prev*, **14**, 413-7.

Gao LL, Huang XE, Zhang Q, et al (2011). A Cisplatin and vinorelbine (NP) regimen as a postoperative adjuvant chemotherapy for completely resected breast cancers in China: final results of a phase II clinical trial. *Asian Pac J Cancer Prev*, **12**, 77-80.

Gong P, Huang XE, Chen CY, et al (2012). Comparison on complications of peripherally inserted central catheters by ultrasound guide or conventional method in cancer patients. *Asian Pac J Cancer Prev*, **13**, 1873-5.

Gu M, Li SY, Huang XE, et al (2013). A phase II study on continuous infusional paclitaxel and 5-Fu as first-line chemotherapy for patients with advanced esophageal cancer. *Asian Pac J Cancer Prev*, **13**, 5587-91.

Huang XE, Li CG, Li Y, et al (2011). Weekly TP regimen as a postoperative adjuvant chemotherapy for completely resected breast cancer in China: final result of a phase II trial. *Asian Pac J Cancer Prev*, **12**, 2797-800.

Huang XE, Wei GL, Huo JG, et al (2013). Intrapleural or intraperitoneal lobaplatin for treatment of patients with malignant pleural effusion or ascites. *Asian Pac J Cancer Prev*, **14**, 2611-4.

Jiang Y, Huang XE, Yan PW, et al (2010). Validation of treatment efficacy of a computer-assisted program for breast cancer patients receiving postoperative adjuvant chemotherapy.*Asian Pac J Cancer Prev*, **11**, 1059-62.

Karpeh MS, Kelsen DP, Tepper JE (2001). Cancer of the stomach. In DeVita VTJr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology, 6th edition. Philadelphia, PA: Lippincott, Williams and Wilkins, 1092-126.

Kim JH, Lee KW, Jung Y, et al (2005). Cytotoxic effects of pemetrexed in gastric cancer cells. Cancer Sci, **96**, 365-71.

Kim YH, Chung HC, Kang WK, et al (2008). Pemetrexed and cisplatin in patients with advanced gastric cancer: a Korean cancer study group multicenter phase II study. *Cancer Chemother Pharmacol*, **62**, 263-70.

Li CG, Huang XE, Li Y, et al (2011). Clinical observations on safety and efficacy of OxyContin® administered by rectal route in treating cancer related pain. *Asian Pac J Cancer Prev*, **12**, 2477-8.

Li CG, Huang XE, Xu L, et al (2012). Clinical application of serum tumor associated material (TAM) from non-small cell lung cancer patients. *Asian Pac J Cancer Prev*, **13**, 301-4.

Li CG, Huang XE, Li Y, et al (2011). Phase II trial of irinotecan plus nedaplatin (INP) in treating patients with extensive stage small cell lung cancer. *Asian Pac J Cancer Prev*, **12**, 487-90.

Li Y, Yan PW, Huang XE, et al (2011). MDR1 gene C3435T polymorphism is associated with clinical outcomes in gastric cancer patients treated with postoperative adjuvant chemotherapy. *Asian Pac J Cancer Prev*, **12**, 2405-9.

Liu J, Huang XE, Tian GY, et al (2013). Phase II Study on Safety and Efficacy of Yadanzi® (Javanica oil emulsion injection) Combined with Chemotherapy for Patients with Gastric Cancer. *Asian Pac J Cancer Prev*, **14**, 2009-12.

Liu W, Li SY, Huang XE, et al (2012). Inhibition of tumor growth in vitro by a combination of extracts from rosa roxburghii tratt and fagopyrum cymosum. *Asian Pac J Cancer Prev*, **13**, 2409-14.

Liu YC, Zhou SB, Gao F, et al (2013). Chemotherapy and Late Course Three Dimensional Conformal Radiotherapy for Treatment of Patients with Stage III Non- small Cell Lung Cancer. *Asian Pac J Cancer Prev*, **14**, 2663-5.

Lu YY, Huang XE, Xu L, et al (2013). Potential Predictors of Sensitivity to Pemetrexed as First-line Chemotherapy for Patients with Advanced Non-Squamous NSCLCs. *Asian Pac J Cancer Prev*, **14**, 2005-8.

Martin M (2006). Clinical experience with pemetrexed in breast cancer. *Semin Oncol*, **33**, S15-18.

Ohtsu A (2008). Chemotherapy for metastatic gastric cancer:past, present, and future. *J Gastroenterol*, **43**, 256-64.

Parkin DM, Bray F, Ferlay J et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Parkin DM, Bray FI, Devesa SS (2001). Cancer burden in the year 2000. The global picture. *Eur J Cancer*, **37**, S4-66.

Pozzo C, Barone C (2008). Is there an optimal chemotherapy regimen for the treatment of advanced gastric cancer that will provide a platform for the introduction of new bio-logical agents? *Oncologist*, **13**, 794-806.

Rollins KD, Lindley C (2005). Pemetrexed: a multitargeted antifolate. *Clin Ther*, **27**, 1343-82.

Ross P, Nicolson M, Cunningham D, et al (2002). Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol*, **20**, 1996-2004.

Shu J, Li CG, Liu YC, et al (2012).Comparison of Serum Tumor Associated Material (TAM) with Conventional Biomarkers in Cancer Patients. *Asian Pac J Cancer Prev*, **13**, 2399-403.

Sun JM, Lee KW, Kim JH, et al (2009). Efficacy and toxicity of pemetrexed as a third-line treatment for non-small cell lung cancer. *Jpn J Clin Oncol*, **39**, 27-32.

Sun MQ, Meng AF, Huang XE, et al (2013). Comparison of psychological influence on breast cancer patients between breast-conserving surgery and modified radical mastectomy. *Asian Pac J Cancer Prev*, **14**, 149-52.

Wagner AD, Unverzagt S, Grothe W, et al (2010). Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev*, **3**, CD004064.

Wu XY, Huang XE, You SX, et al (2013). Phase II Study of Pemetrexed as Second or Third Line Combined Chemotherapy in Patients with Colorectal Cancer. *Asian Pac J Cancer Prev*, **14**, 2019-22.

Xu HX, Huang XE, Li Y, et al (2011). A clinical study on safety and efficacy of Aidi injection combined with chemotherapy. *Asian Pac J Cancer Prev*, **12**, 2233-6.

Xu HX, Huang XE, Qian ZY, et al (2011). Clinical observation of Endostar® combined with chemotherapy in advanced colorectal cancer patients. *Asian Pac J Cancer Prev*, **12**, 3087-90.

Xu JW, Li CG, Huang XE, et al (2011). Ubenimex capsule improves general performance and chemotherapy related toxicity in advanced gastric cancer cases. *Asian Pac J Cancer Prev*, **12**, 985-7.

Xu T, Xu ZC, Zou Q, Yu B, Huang XE (2012).P53 Arg72Pro polymorphism and bladder cancer risk--meta-analysis evidence for a link in Asians but not Caucasians. *Asian Pac J Cancer Prev*, **13**, 2349-54.

Xu X, Wang L, Xu HQ, et al (2013). Clinical Comparison between Paclitaxel Liposome (Lipusu®) and Paclitaxel for Treatment of Patients with Metastatic Gastric Cancer. *Asian Pac J Cancer Prev*, **14**, 2591-4.

Yan PW, Huang XE, Jiang Y, et al (2010). A clinical comparison on safety and efficacy of Paclitaxel/Epirubicin (NE) with Fluorouracil/Epirubicin/Cyclophosphamide (FEC) as postoperative adjuvant chemotherapy in breast cancer. *Asian Pac J Cancer Prev*, **11**, 1115-8.

Yan PW, Huang XE, Yan F, et al (2011). Influence of MDR1 gene codon 3435 polymorphisms on outcome of platinum-based chemotherapy for advanced non small cell lung cancer. *Asian Pac J Cancer Prev*, **12**, 2291-4.

Yin HT, Tian QZ, Guan L (2013). In vitro and in vivo evaluation of the antitumor efficiency of resveratrol against lung cancer. *Asian Pac J Cancer Prev*, **14**, 1703-6.

Yin HT, Zhang DG, Wu XL (2013). In vivo evaluation of curcumin-loaded nanoparticles in a A549 xenograft mice model. *Asian Pac J Cancer Prev*, **14**, 409-12.

Yu DS, Huang XE, Zhou JN, et al (2012). A Comparative study on the value of anal preserving surgery for aged people with low rectal carcinoma in Jiangsu, China. *Asian Pac J Cancer Prev*, **13**, 2339-40.

Zhan YP, Huang XE, Cao J (2012). Clinical study on safety and efficacy of Qinin® (cantharidin sodium) injection combined with chemotherapy in treating patients with gastric cancer. *Asian Pac J Cancer Prev*, **13**, 4773-6.

Zhan YP, Huang XE, Cao J (2012). Clinical safety and efficacy of Kanglaite® (Coix Seed Oil) injection combined with chemotherapy in treating patients with gastric cancer. *Asian Pac J Cancer Prev*, **13**, 5319-21.

Zhang LQ, Huang XE, Wang J (2011). The cyclin D1 G870A polymorphism and colorectal cancer susceptibility: a meta-analysis of 20 populations. *Asian Pac J Cancer Prev*, **12**, 81-5.

Zhang XZ, Huang XE, Xu YL, et al (2012). Phase II study on voriconazole for treatment of Chinese patients with malignant hematological disorders and invasive aspergillosis. *Asian Pac J Cancer Prev*, **13**, 2415-8.

Zhou JN, Huang XE, Ye Z, et al (2009). Weekly paclitaxel/ Docetaxel combined with a paltinum in the treatment of advanced non-samll cell lung cancer: a study on efficacy, safety and pre-medication. *Asian Pac J Cancer Prev*, **10**, 1147-50.