RESEARCH ARTICLE

Potential Predictors of Sensitivity to Pemetrexed as First-line Chemotherapy for Patients with Advanced Non-Squamous NSCLCs

Yan-Yan Lu[1], Xin-En Huang[1]*, Lin Xu[2]*, De-Gan Liu[3], Jie Cao[1], Xue-Yan Wu[1], Jin Liu[1], Jin Xiang[4]

Abstract

Background: Pemetrexed (PEM) is effective in first-line treatment for patients with non-squamous non-small cell lung cancer (NSCLC). However there are currently no definitive determinants to certify which patients could benefit from PEM. To improve the efficacy of PEM combined with platinum as first-line therapy for advanced non-squamous NSCLC, we conducted this retrospective study to detect potential determinants of this regimen. Methods: We recruited 109 patients with advanced non-squamous NSCLC who received PEM with a platinum as first-line therapy from June 2006 to February 2013 in Jiangsu Cancer Hospital. Multiple variables (age, sex, smoking, degree of cell differentiation, hemoglobin, platinum drugs combined, positions of metastasis) were selected. Logistic regression analysis was used to analyse relationships between these variables and tumor response. Result: In univariate analysis, we found that age and platinum significantly influenced the results of PEM therapy ($P<0.05$). In multivariable analysis, no factors were independently significant. Conclusion: Our analysis did not suggest that the age, sex, metastasis of liver or other organs, hemoglobin, smoking history and pathological differentiation are associated with the response of PEM. We should conduct further analyses with larger sample size to reconfirm this issue.

Keywords: Pemetrexed - non-squamous NSCLC - platinum chemotherapy - age - China

Asian Pacific J Cancer Prev, **14 (3)**, 2005-2008

Introduction

According to WHO statistics, the incidence and fatality rate of lung cancer increase year by year. And in China, more than 75% of patients with non-small cell lung cancer (NSCLC) present with locally advanced (stage IIIB) or metastatic (stage IV) disease at diagnosis (Zhou et al., 2011). For patients in this setting, platinum-based chemotherapy is recommended as first-line treatment according to current guideline (Pfister et al., 2003). Some studys showed non-inferior efficacy and better tolerability for PEM plus cisplatin than for cisplatin plus other chemotherapy agents eg.:gemcitabine or docetaxel especially for patients with adenocarcinoma (Reck et al., 2009; Scagliotti et al., 2009; Klein et al., 2010). PEM is an antifolate that inhibits multiple enzymes involved in purine and pyrimidine synthesis. The mechanism of action consists of the inhibition of three key enzymes in the folate metabolic pathway, including thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT) (Giovannetti et al., 2005). This mechanism leads to depletion of fully reduced folate, ultimately resulting in disruption of nucleotide synthesis for both pyrimidines and purines. Pemetrexed, once in the cell, is an excellent substrate for polylpolyglutamate synthetase, leading to extensive intracellular polyglutamate derivates that are more potent inhibitors of the described enzymes. Polyglutamated pemetrexed is retained intracellularly longer than the parent compound, resulting in more prolonged cytotoxic effects (E.Esteban et al., 2009). It is reported that resistance to PEM is correlated with high pre-treatment TS, GARFT ,and DHFR expression in NSCLC cell (U. Eismann et al., 2006).TS expression is regarded as the most meaningful predictor for sensitivity or resistance to PEM in fresh tumor tissue. But for patients with advanced NSCLC, no enough tumor tissue is available for the detection of TS, GARFT, and DHFR expression. And limited by the condition of experiment in different hospitals and regions, the test result cannot be in full compliance with the actual situation. Thus at present, PEM is given to patients with advanced NSCLC, regardless of whether TS, GARFT ,and DHFR is over-expressed. In an attempt to indentify predictors of clinical indictors for sensitivity of PEM and

*[1]Department of Chemotherapy, [2]Department of Thoracic Surgery, [4]Department of Research, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, Nanjing, [3]Department of Oncology, Xinghua People's Hospital, Xinghua, Jiangsu, China *For correspondence: huangxinen06@yahoo.com.cn, xulin_83@yahoo.cn*

Table 1. Univariate Analysis of Features Associated with Sensitivity to Pemetrexed

Variable	Response (n=99)	Non-response (n=10)	OR (95%CI)
Sex			
Male	60	7	0.66 (0.16-2.70)
Female	39	3	
Age			
<65	26	7	0.15 (0 .04-0.63)*
≥65	73	3	
Differentiation			
Well	69	5	2.30 (0 .62-8.54)
Not well	30	5	
Smoking			
Yes	12	0	1.38 (0.16-11.75)
No	87	20	
Paltinum combined			
DDP	58	0	0.56 (0.35-0.89)*
NDP	8	3	
LBP	2	0	
CBP	31	7	
Hb			
≥120	65	8	0 .48 (0.10-2.38)
<120	34	2	
Bone metastasis			
Yes	51	6	0.71 (0 .19-2.67)
No	48	4	
Lung metastasis			
Yes	54	3	2.80 (0.68-11.46)
No	45	7	
Liver metastasis			
Yes	11	1	1.125 (0.13-9.75)
No	88	9	
Pleura metastasis			
Yes	40	4	1.02 (0.27-3.84)
No	59	6	
Adrenal glands metastasis			
Yes	6	2	0.26 (0.05-1.94)
No	93	8	
Brain metastasis			
Yes	19	2	0.95 (0.19-4.84)
No	80	8	
Distant lymph node metastasis			
Yes	23	2	1.21 (0.24-6.11)
No	76	8	

design a model for the judgment of PEM response, we conduct this study to identify factors that could indentify patients who could mostly benefit from PEM therapy.

Materials and Methods

Patients

Patients were required to be pathologically/cytologically diagnosed with advanced non-squamous NSCLC in Jiangsu Cancer Hospital & Research Institute from June 2006 to February 2013, without history of chemotherapy; to sign an informed consent before treatment; to have a score of karnofsky performance status ≥ 70; to be 25 to 75 years of age. Other eligibility criteria included: adequate hematological (white blood cell count > 3.0×10^9 and platelet count > 150×10^9), liver (bilirubin and transaminases < 1.5 times the upper normal limit) and renal function (creatinine leval < 1.5 times the upper normal limit); patients were excluded from this study if they failed to complete two cycles of chemotherapy, or with any serious medical or psychiatric condition, or other malignancies. Pregnant or lactating women are also excluded from this study.

We retrospectively reviewed the records, pathological reports, and imaging studies of eligible patients and then compared the characteristics of responders with those of none-responders. These groups of patients were analyzed for significance of sex, age, smoking history, pathological differentiation, platinum combined, hemoglobin and sites of metastasis.

Treatment

PEM was given at a dose of 500 mg/m^2 with a platinum that is recommended by NCCN. All the patient received two cycles of therapy and 21 days as a cycle.

Radiologic Evaluation

For all patients, we reviewed the imaging studies performed at the initiation of therapy. Follow-up imaging was performed after two cycles of chemotherapy. All imaging was reviewed by one thoracic radiologist. Non-responders were identified by clinical reports for hospital radiologic studies. We classified the therapeutic results as complete or partial remission and stable or progressive disease according to the response evaluation criteria for solid tumors (Therasse et al., 2000).

Statistical Methods

We investigated the associations between sensitivity to pemetrexed and patients characteristics. Potential prognostic factors explored included sex, age, smoking history, the level of pathological differentiation, platinum combined, hemoglobin and sits of metastasis. The primary objective was to identify the factors associated with response to PEM. The associations between response and the covariates were assessed using univariate logistic regression analysis. All variables in the univariate analysis were then included in multivariable logistic regression model with pemetrexed response as the dependent variable.

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; Li et al., 2012; Yu et al., 2012).

Results

One hundred and nine patients with advanced NSCLC who had no history of chemotherapy accepted PEM with a platinum as first line chemotherapy for two cycles. The overall observed response rate was 83%. Table 1 lists patient demographics and the results of potential prognostic factors for PEM sensitivity using

Table 2. Multivariable Analysis of Features Associated with Sensitivity to Pemetrexed

Variable	OR (95% CI)
Sex	1.59 (0.36-6.95)
Age	0.98 (0.90-1.06)
Level of Differentiation	3.43 (0.73-16.11)
Paltinum combined	0.75 (0.39-1.44)
Smoking	0.90 (0.07-11.10)
Bone metastasis	2.90 (0.36-23.37)
Lung metastasis	0.61 (0.13-2.83)
Liver metastasis	1.47E8 (...)
Adrenal glands metastasis	0.42 (0.02-10.00)
Brain metastasis	0.67 (0.08-5.40)
Distant lymph node metastasis	0.56 (0.05-5.88)
Hb	0.00 (...)
Constant	5.98E9 (...)

univariate logistic regression analysis. Seventy percent of patients were older than 65 and 68% well differentiated adenocarcinoma. Twenty percent of patients had liver metastases. We found that age and platinum were significant in predicting the sensitivity of PEM ($p<0.05$). Then all the factors were tested in a multivariable logistic regression analysis. The result showed in Table 2. No significant difference in response rate to PEM was found in those potential predictors

Discussion

Cisplatin-based chemotherapy for patients with advanced NSCLC results in a small but statistically significant improvement in survival, as compared with supportive care. Combination of a platinum plus a new agent continues to be the standard of care (Marino et al., 1994).

PEM is an effective and well tolerated chemotherapeutic agent. Based on previous studies, it is considered that PEM is proper for patients who were pathologically diagnosed with lung adenocarcinoma (Rodrigues-Pereira et al., 2011). However, we think it is important to clarify patients who could mostly benefit from this treatment. PEM is recommended for patients with advanced NSCLC and adenocarcinoma, regardless of whether TS, GARFT, and DHFR is over-expressed. Considering the general characteristics of patients with advanced NSCLC and the pharmacokinetics of PEM, we intend to clarify predictors of response for this regimen and we hypothesis that sex, age, differentiation level, etc. could be possible predictors. Age at diagnosis influences survival, and women with squamous or anaplastic tumors have a better prognosis than men with the same pathological types(Rossing et al., 1982). PEM inhibits the folate dependent enzymes (although all the patients were given the standard vitamin supplementation). It may also interfere the metabolism of hemoglobin. And hemoglobin, age and sex may reflect the general condition of a patient, so we included sex, age, tumor differentiation in logistic regression model. It was reported that cisplatin-based chemotherapy is slightly superior to carboplatin-based chemotherapy in terms of response rate (Ardizzoni et al., 2007), suggesting that platinum could be a factor influencing the response of PEM. In addition, cigarette smoking is reported to change induction of hepatic microsomal enzymes in man and animals (Jusko, 1978), indicating that smoking history and cancer metastasis especially liver metastasis could associated with metabolism of chemotherapeutic agents. Therefore, impact of platinum, smoking habit and live metastasis was also estimated.

In this study, we found that age and platinum had significant impact on the response of PEM therapy by univariate analysis. However, all the factors imposed no significantly different influence on response rate of PEM therapy according to multivariable analysis. Our study provided a research direction. Considering the sample size of this study is not large enough to detect minor difference of these variables regarding the influence on the response, a further study containing sufficient number of cases is needed to re-confirm this result.

Acknowledgements

Dr. Xin-En Huang is supported by Traditional Chinese Medicine Scientific Research Project (LZ11091) and Jiangsu Province fourth stage “333 high- level Personnel Training Project” third levels of talent cultivating object.

References

Ardizzoni A, Boni L, Tiseo M, et al (2007). Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer, an individual patient data meta-analysis. *J Natl Cancer Inst*, **99**, 847-57.

Eismann U, Oberschmidt O, Ehnert M, et al (2005). Pemetrexed: mRNA expression of the target genes TS, GARFT and DHFR correlates with the in vitro chemosensitivity of human solid tumors. *Int J Clin Pharmacol Ther*, **43**, 567-9.

Esteban E, Casillas M, Cassinello A, et al (2009). Pemetrexed in first-line treatment of non-small cell lung cancer. *Cancer Treat Rev*, **35**, 364-73

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.

Giovannetti E, Mey V, Nannizzi S, et al (2005). Cellular and pharmacogenetics foundation of synergistic interaction of pemetrexed and gemcitabine in human non-small-cell lung cancer cells. *Mol Pharmacol*, **68**, 110-8.

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

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.

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.

Jusko WJ (1978). Role of tobacco smoking in pharmacokinetics. *J Pharmacokinet Biopharm*, **6**, 7-39.

Klein R, Wielage R, Muehlenbein C, et al (2010). Cost-effectiveness of pemetrexed as first-line maintenance therapy for advanced nonsquamous non-small cell lung cancer. *J Thorac Oncol*, **5**, 1263-72.

Li CG, Huang XE, Li Y, Lu YY (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, Li Y, Lu YY (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 (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, Li CG (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 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.

Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F (1994). Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. *Chest*, **106**, 861-5.

Pfister DG, Johnson DH, Azzoli CG, et al (2004). American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline, update 2003. *J Clin Oncol*, **22**, 330-53.

Reck M, von Pawel J, Zatloukal P, et al (2009). Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer, AVAil. *J Clin Oncol*, **27**, 1227-34.

Rodrigues-Pereira J, Kim JH, Magallanes M, et al (2011). A randomized phase 3 trial comparing pemetrexed/carboplatin and docetaxel/carboplatin as first-line treatment for advanced, nonsquamous non-small cell lung cancer. *J Thorac Onco*l, **6**, 1907-14.

Rossing TH, Rossing RG (1982). Survival in lung cancer. An analysis of the effects of age, sex, resectability, and histopathologic type. *Am Rev Respir Dis*, **126**, 771-7.

Scagliotti G, Hanna N, Fossella F, et al (2009). The differential efficacy of pemetrexed according to NSCLC histology, a review of two Phase III studies. *Oncologist*, **14**, 253-63.

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.

Sozzi G, Sard L, De Gregorio L, et al (1997). Association between cigarette smoking and FHIT gene alterations in lung cancer. *Cancer Res*, **57**, 2121-3.

Therasse P, Arbuck SG, Eisenhauer EA, et al (2000). 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*, **92**, 205-16.

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.

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.

Yu DS, Huang XE, Zhou JN (2012). 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.

Zhang LQ, Huang XE, Wang J, et al (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.

Zhou Q, Shi Y, Chen J, et al (2011). [Long-term survival of personalized surgical treatment of locally advanced non-small cell lung cancer based on molecular staging]. *Zhongguo Fei Ai Za Zhi*, **14**, 86-106.