RESEARCH ARTICLE

Pemetrexed as a Component of First-, Second- and Third-line Chemotherapy in Treating Patients with Metastatic Lung Adenocarcinoma

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Abstract

Purpose: The current research was conducted to investigate the efficacy and safety of pemetrexed given continuously as a basement agent for first-, second- to third line chemotherapy of patients with metastatic lung adenocarcinoma. Patients and Methods: Patients with metastatic lung adenocarcinoma who were diagnosed in Jiangsu Cancer Hospital and Research Insitute, were enrolled. All received pemetrexed 500 mg/m^2 (intravenous; on day 1), and another chemotherapieutic agent every 3 weeks until disease progression, or intolerable toxicity. Then the patients were changed to a second line chemotherapy that was still based on pemetrexed 500 mg/m^2 and another chemotherapeutic agent differing from the first line example, until disease progression, or intolerable toxicity. When third line chemotherapy was needed, pemetrexed 500 mg/m^2 and another new chemotherapeutic agent were combined until disease progression. Evaluation of efficacy was conducted after two cycles of chemotherapy using the Response Evaluation Criteria for Solid Tumors. Toxicity was recorded according to NCI Criteria for Adverse Events version 3.0. Results: From January 2010 to September 2013, 15 patients were enrolled. Their median age was 56 years (range 43 to 77 years). Eight patients were male and 7 female. Five patients (33.3%) achieved PR, while 6 patients (40.0%) remained stable, no CR on first line; and 1 PR (7.7%), 5 stable (38.5%) were recorded when pemetrexed was ordered in second line; 5 patients (41.7%) were stable after pemetrexed was combined in third line; no complete response was observed. Main side effects were grade 1 to 2 neutrophil suppression and thrombocytopenia. Other toxicities included elevated transaminase and oral mucositis, but no treatment related death occurred. Conclusions: Pemetrexed continuously as a basement agent from first-, second- to third line chemotherapy is mildly effective in treating patients with metastatic lung adenocarcinoma with tolerable toxicity.

Keywords: Pemetrexed - lung adenocarcinoma - first-third line therapies - toxicity - efficacy

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Introduction

Cisplatin-based chemotherapy for patients with advanced NSCLC results in mild improvement in survival, as compared with supportive care. Combination of a platinum from first-, second- to third line therapy plus another chemotherapeutic agent continues to be a standard of care (Marino et al., 1994). However, side effects of platinum is also significant, e.g., nausea, vomiting, and renal toxicity, and is the reason of discontinuation of chemotherapy. On this background, we consider that cisplatin could be recommended as a component of first line chemotherapy (NCCN guideline, 2013), but if failed, should not continuously be a component of second- and even third-line agent in treating patients with lung adenocarcinoma.

Pemetrexed (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). The tolerability of PEM is good, thus is recommended for patients with advanced NSCLC and adenocarcinoma, regardless of whether TS, GARFT, and DHFR is over-expressed. Considering general characteristics of patients with advanced NSCLC and the pharmacokinetics and well tolerability of PEM, we hypothesize that pemetrexed as a component of first-, second- and third line chemotherapy could be a reasonable regimen in treating patients with lung adenocarcinoma.

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Materials and Methods

Patient eligibility

Eligible patients should be histologically confirmed adenocarcinoma of lung with clinical evidence of metastatic disease. Other eligible criteria include: age≥18 years; adequate bone marrow (platelets≥100×109 cells/l, absolute neutrophil count≥1.5×109 cells/l), hepatic (total bilirubin ≤ 2×the upper limit of normal; aspartatetransaminase ≤ 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; and another chemotherapieutic agent (e.g., a platinum, paclitaxel, docetaxel, ifosfamide, irinotecan, etoposide, etc.) every 3 weeks until disease progression, or intolerable toxicity. Then, the patients were changed to second line chemotherapy that was based on pemetrexed 500 mg/m^2 and another chemotherapieutic agent different from the first line until disease progression, or intolerable toxicity. When third line chemotherapy was needed, pemetrexed 500 mg/m^2 and a chemotherapieutic agent different from first and second line was combined until disease progression. Antiemetics were given with chemotherapy on days 1. All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version2.0) (National Cancer Institute, 1998).

Table 1. General Characteristics of Patients (n=15)

Characteristic	Patients, n (%)
Age, years	
Median	56
Range	43-77
Sex	
Male	8 (53%)
Female	7 (47%)
ECOG performance status	
≤2	13 (87%)
>2	2 (13%)
Number of organs involved	
1	7 (53%)
≥2	8 (47%)
Sites of metastases	
Lymph node	10 (33%)
Liver	0 (0%)
Lung	6 (20%)
Bone	9 (30%)
Others	5 (17%)
Pemetrexed based Chemotherapy	
First line	15
Second line	13
Third line	12

ECOG, Eastern Cooperative Oncology Group

Table 2. Chemotherapy

Chemotherapy
First Line Chemotherapy
PEM (500 mg/m^2) d1+DDP (20 mg/m^2) d1-5
PEM (500 mg/m^2) d1+CBP (300 mg/m^2) d2
Second line Chemotherapy
PEM (500 mg/m^2) d1+Decetaxel (40 mg/m^2) d1,8
PEM (500 mg/m^2) d1+Ifosfamide (1-1.5 g/m^2) d1-3 and d8-9
Third line Chemotherapy
PEM (500 mg/m^2)d1+CPT-11 (80 mg/m^2) d1,8
PEM (500 mg/m^2)d1+ lobaplatin (30 mg/m^2) d2

PEM, Pemetrexed

Research experience

We have enough experience in conducting medical researches, and have published some results elsewhere (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; Liu et al., 2012; Gu et al., 2013; Li et al., 2012; Shu et al., 2012; Zhan et al., 2012; Zhan et al., 2012; Xu et al., 2012; Xu et al., 2012; Yu et al., 2012; Zhang, et al., 2012; Zhang et al., 2012; Chen et al., 2013; Dai et al., 2013; Deng et al., 2013; Huang et al., 2013; Liu et al., 2013; Liu et al., 2013; Liu et al., 2013; Lu et al., 2013; Sun et al., 2013; Wei et al., 2013; Wu et al., 2013; Yang et al., 2013; Yin et al., 2013; Yin et al., 2013).

Results

Patients

A total of 15 patients were enrolled from January 2010 to September 2013. All patients received at least one systemic chemotherapy. All patients had adenocarcinoma of the lung. General characteristics of patients were listed in Table 1. Fifteen patients received pemetrexed based

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

Type	Haematological Toxicities	None-Haematological Toxicities
Grade 1	2	3
Grade 2	9	4
Grade 3	2	2
Grade 4	0	0

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

combination therapy as first line, 13 as second, and 12 as third line chemotherapy (Table 2).

Efficacy

Fifteen patients completed at least 2 cycles of chemotherapy on first line chemotherapy, and were evaluated according to study protocol. Overall, 5 patients (33.3%) achieved PR, while 6 patients (40.0%) remained stable, no CR on first line; and 1 PR (7.7%), 5 stable (38.5%)were recorded when pemetrexed was ordered in second line; 5 patients (41.7%) got stable after pemetrexed was combined in third line; no complete response was observed (Table 2).

Toxicity

Main side effects were grade 1 to 2 neutrophil suppression and thrombocytopenia. Other toxicities included elevated transaminase and oral mucositis, no treatment related death occurred (Table 3).

Discussion

According to WHO statistics, the incidence and motality rate of lung cancer increases 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 compared with cisplatin plus other chemotherapeutic 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 (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 (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. And in the field of maintenance therapy for advanced NSCLC, in line with the evidence currently available, it represents a treatment option. In real practice, maintenance therapy is recommended to patients without disease progression or persistent chemotherapy-induced toxicities after several cycles of first-line chemotherapy, however, with good performance status. Two different strategies (switch or continuation maintenance) are available. The hazard ratio for PFS is in the range of 0.6 to 0.7 in most of the trials for both strategies. OS is only significantly improved in the SATURN (Cappuzzo et al., 2010) and JMEN (Ciuleanu et al., 2009) switch-maintenance trials, and in the PARAMOUNT trial (Paz-Ares et al., 2012) with the continuation strategy. These were the only three trials with a reasonable size (539 to 889 patients) to enable adequately powered comparisons. No powered comparative trials of maintenance with different chemotherapy drugs or targeted agents have been conducted, thus, no conclusive data are available yet about the potential advantage of any given therapy. The potential advantages and disadvantages, including toxicities, of continuation or switch maintenance is not sure. The PARAMOUNT trial revealed that pemetrexed maintenance therapy could improve efficacy over placebo following four courses of cisplatin/pemetrexed (Paz-Ares et al., 2011). The primary objective of this study, PFS, was improved in the pemetrexed maintenance arm compared with placebo (4.1 vs. 2.8 months, HR 0.62), and OS was also significantly improved (13.9 vs. 11 months, HR 0.78) (Paz-Ares et al., 2012).

Recent placebo-controlled trials evaluated the role of pemetrexed as maintenance therapy for patients with advanced NSCLC following disease control with four cycles of platinum-based therapy and suggested that pemetrexed maintenance significantly improved PFS (4.0 vs. 2.0 months; HR 0.60) and OS (13.4 vs. 10.6 months; HR 0.79) (Ciuleanu et al., 2009; Cappuzzo et al., 2010). Prolonging treatment duration has shown to prolong PFS, without a clinically significant effect on survival, at the cost of relevant toxicity, particularly with platinum agents and taxanes (Lima et al., 2009). This is the reason why we try to develop a regimen that is tolerable to patient at this point. However, no study focused on pemetrexed as a basement of combined treatment from first to second and third line chemotherapy. Our study demonstrated that 5 patients (33.3%) achieved PR, while 6 patients (40.0%) remained stable, on first line; and 1 PR (7.7%), 5 stable (38.5%)were recorded when pemetrexed was ordered in second line; 5 patients (41.7%) got stable after pemetrexed

was combined in third line. Main side effects were Grade 1 to 2 neutrophil suppression and thrombocytopenia. Other toxicities included elevated transaminase and oral mucositis, no treatment related death occurred.

In conclusion, our study suggested that pemetrexed continuously as a basement agent from first-, second- to third line chemotherapy is mildly effective in treating patients with metastatic lung adenocarcinoma with tolerable toxicity.

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