

The Clinical Investigation of Pemetrexed Plus Carboplatin as an Active and Tolerable Treatment Plan in Chinese Elderly Patients with Advanced Lung Adenocarcinoma

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ABSTRACT

The standard chemotherapy for Chinese elderly patients with non-small cell lung cancer (NSCLC) remains undefined. The study was to evaluate the therapeutic effects as well as side effects of pemetrexed plus carboplatin regimen as the first-line therapy for Chinese elderly patients with advanced lung adenocarcinoma. Twenty-three Chinese elderly patients (male 14 and female 9, average age 73.7 years, range 70 - 81 years) with advanced lung adenocarcinoma received pemetrexed plus carboplatin as the first-line therapy, in detail, pemetrexed 500 mg/m² and carboplatin AUC 5 mg/ml/m² were given intravenously on day 1. The treatment was repeated everyday in the 21 days cycle. Therapeutic effects were evaluated at least after two cycles of treatment. The remission rate, disease control rate, time to progression and overall survival were observed. The results showed that all the cases were valid for response evaluation, with the complete remission 0 case, partial remission 8 cases, stabilize disease 9 cases and progression disease 6 cases. The remission rate (including complete remission and partial remission) was 34.8%, disease control rate 73.9%, the time to progression was 5.8 months and the overall survival 13.7 months. There showed the positive relationship between the curative effects (either time to progression or overall survival) and chemotherapy cycles. The main toxicities were bone marrow suppression, nausea and vomiting. There was no chemotherapy-related death. The data suggested that the combination regimen with pemetrexed plus carboplatin is an active and tolerable treatment plan for Chinese elderly patients with advanced lung adenocarcinoma, in which the side effects were tolerable and manageable.

Keywords: Pemetrexed, Carboplatin, Chinese Elderly Patient, Lung Adenocarcinoma

1. Introduction

For the past few years, the incidence rate and fatality rate of lung cancer had improved to the first place in the various kinds of malignant tumors in China. More than 50% lung cancer patients were been made a definite diagnosis of pulmonary adenocarcinoma in advanced stage who had a 10% - 15% five-year survival rate and principally treated with chemotherapy. Meanwhile, with China stepping into the aging society, more than 50% lung cancer preliminary diagnosis patients were aged more than 65 years and more than 30% patients were aged more than 70 years [1]. Single drug chemotherapy is the standard recommended therapy plan for the old

aged lung cancer patients [2-5]. However, the standard double drug combination, for example the pemetrexed plus carboplatin regimen, to treat the lung cancer is absent nowadays. Depending on the anti-cancer drug clinical characters, the present study was to evaluate the therapeutic effects as well as side effects of the pemetrexed plus carboplatin regimen as an active and tolerable treatment plan for Chinese elderly patients with advanced lung adenocarcinoma.

2. Materials and Methods

2.1. Patient Selection

We selected 23 Chinese patients of advanced lung ade-

nocarcinoma in our hospital randomly by principle of statistics from March 2005 to May 2007, who had signed the consent form, male 14 cases and female 9 cases, 70 - 81 years old that average was at 73.7 years (Table 1). All the patients, whose Eastern Cooperative Oncology Group (ECOG) score was less than 2 points and expecting survival period less than 3 months, were diagnosed by the pathological method. Except for the objective lesions being observed and evaluated, it was not observed clearly the apparent for emphysema, respiratory function in-compensation and lesions in the heart, liver and kidney.

2.2. Therapeutic Methods

Pemetrexed disodium for injection 500 mg/m² was dissolved into 100 ml physiological sodium, and carboplatin AUC for injection 5 mg/ml/m² (with physiological sodium) intravenously on day 1. Treatment was repeated everyday in the 21-days cycle. Therapeutic effects were evaluated at least after two treatment cycles. At least 2 cycles of chemotherapy would be appended when the first therapeutic effect evaluation was the complete remission (CR)/partial remission (PR)/stabilize (SD). Ac-

ording to the physical condition, the patient would be determined whether the additional chemotherapy, in which 8 cycles was the upper limit.

Granisetron, a 5-HT₃ receptor antagonist 3mg was used intravenously at 30 min before the chemotherapy to prevent vomiting. The blood routine was checked every week and the electrocardiogram, liver and kidney function were examined before each chemotherapy cycle. If the III grade or above adverse reaction appeared in the previous chemotherapy cycle, the drug dosage was reduced 25% in the next chemotherapy cycle. If the III-IV grade adverse reaction consecutively appeared in double chemotherapy cycles, the treatment protocols should be cancelled. If the clinical III-IV grade bone marrow depression appeared during the treatment period, granulocyte colony-stimulating factor (G-CSF, 75 ug - 150 ug, intramuscular injection) should immediately been used to rise the leucocyte up to 10 × 10⁹/L and the drug dosage been reduced 25% in the next chemotherapy cycle. Dexamethasone (4 mg, oral, bid) should consecutively be used 3 days at the revising day, today and next day during the pemetrexed administration. Folic acid 400 μg

Table 1. The clinical data and curative effect evaluation of Chinese elderly patients with advanced lung adenocarcinoma curing by the pemetrexed plus carboplatin as an active and tolerable treatment plan.

	Gender	Age (year)	Clinical stage ⁺	Curative effect evaluation*	Actual chemotherapy periods	Time to progression	Overall survival
1	male	71	IIIB	PR	7	9.4	15.5
2	female	75	IV	PR	4	6.5	15.0
3	male	71	IV	PD	2	1.5	2.1
4	male	77	IIIB	SD	4	5.0	12.1
5	female	72	IV	PR	5	5.5	20.0
6	female	73	IV	PD	2	1.6	14.8
7	male	70	IV	PR	7	12.7	26.0
8	male	80	IV	SD	5	5.8	13.4
9	male	81	IIIB	SD	6	6.1	18.4
10	male	72	IIIB	PD	2	1.5	2.7
11	female	78	IV	PD	2	1.4	4.5
12	male	76	IV	SD	4	6.4	13.7
13	male	70	IIIB	PR	4	5.5	8.0
14	female	74	IIIB	PD	2	1.7	3.7
15	male	72	IIIB	PR	6	9.0	31.0
16	female	72	IIIB	PD	2	1.6	10.5
17	male	73	IV	SD	5	5.7	10.5
18	male	71	IIIA	PR	8	11.0	20.0
19	female	77	IIIB	SD	4	5.2	17.4
20	female	74	IIIA	PR	4	6.2	15.0
21	male	71	IV	SD	5	7.0	11.1
22	female	73	IIIB	SD	6	7.3	12.8
23	male	72	IIIA	SD	8	9.4	20.5

*Curative effect evaluation: According to the entity tumor evaluation criterion of the response evaluation criteria in solid tumors (RECIST), the cases of lung adenocarcinoma were divided into the remission (CR), partial remission (PR), stabilize (SD) and progression (PD); ⁺Clinical stage: Toxic and adverse reaction were been divided into 0-IV grade depending on World Health Organization (WHO) anticancer drugs standardization.

qd) should consecutively be used 5 days before the 7 days of first pemetrexed administration and during all the cycle. The folic acid administration was cancelled after the 21 days of the pemetrexed administration. Vitamin B₁₂ (1 mg, intramuscular injection) should be used before the 7 days of the first pemetrexed administration and injected per 3 periods later with the pemetrexed administration in the same day.

2.3. Observation and Evaluation Criterion

After 2 - 8 chemotherapy cycles, the 23 Chinese patients of lung adenocarcinoma were divided into the remission (CR), partial remission (PR), stabilize (SD) and progression (PD) according to the entity tumor evaluation criterion of RECIST. Remission rate (RR) = CR + PR, and disease control rate (DCR) = CR + PR + SD. Time to progression (TTP) is calculated from the beginning time of therapy to the lesion appearing time. Overall survival (OS) is calculated from the beginning time of therapy to the death. Toxic and adverse reaction were been divided into clinical 0-IV grade depending on World Health Organization (WHO) anticancer drugs standardization.

2.4. Statistical Treatment

All the steps were completed by SPSS11.0. Kaplan-Meier method was used in the survival analysis and χ^2 -test in comparing the enumeration data and ratio.

3. Results

3.1. Curative Effect Evaluation

After 2 - 8 chemotherapy cycles (average 4.57 cycles and total 105 cycles), the curative effect in all the 23 Chinese patients was the complete remission (CR) 0 case, partial remission (PR) 8 cases, stabilize (SD) 9 cases, progression (PD) 6 cases. The RR was 34.8% and DCR 73.9%; The TTP was 1.4 - 12.7 months (average 5.8 months) and the OS 2.1 - 31months (average 13.7 months) (Table 1). The epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), radiotherapy and traditional Chinese medicine were been used in the cases of the first-line therapy cases and the second-line therapy cases whose pathogenetic condition appeared recurrence.

3.2. The Relationship between Curative Effect and Chemotherapy Cycles

There showed the positive relationship between the curative effects and chemotherapy cycles, *i.e.* the TTP and OS can be prolonged if we gave more chemotherapy cycles to the PS/SD cases after the 2 chemotherapy cycles (Figures 1 and 2).

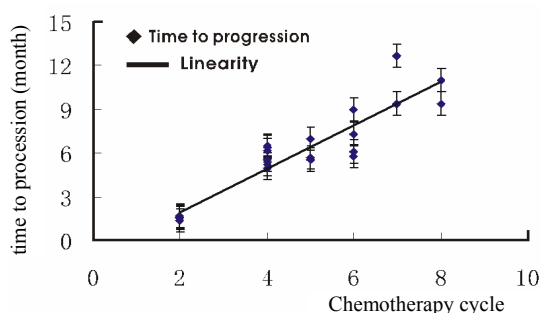


Figure 1. The relationship between the time to procession and chemotherapy cycles in Chinese elderly patients with advanced lung adenocarcinoma curing by the pemetrexed plus carboplatin as an active and tolerable treatment plan.

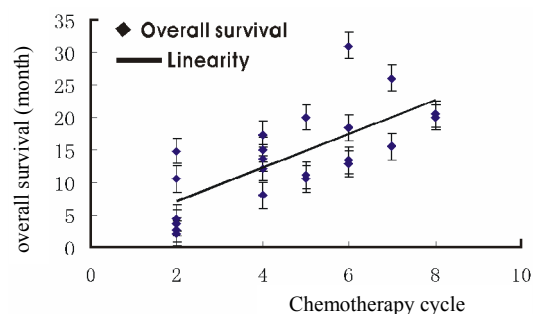


Figure 2. The relationship between the overall survival and chemotherapy cycles in Chinese elderly patients with advanced lung adenocarcinoma curing by the pemetrexed plus carboplatin as an active and tolerable treatment plan.

3.3. Toxic and Adverse Reaction

The main toxicities were the bone marrow suppression and gastrointestinal reaction including nausea and vomiting. Leucocyte reduced 13.0% and thrombocytopenia reduced 4.35% in the cases with clinical III~IV grade. There was no chemotherapy-related death (Table 2). The toxicities were reversible, *i.e.* the pathogenetic conditions got better if the chemotherapy drugs were removed and the symptomatic therapy was given.

4. Discussion

Now, the therapy of lung cancer has stepped into a period of molecule tumor, *i.e.* more and more molecule targeted therapy drugs have been discovered according to the tumorigenesis mechanism, for example, EGFR TKI, cetuximab, bevacizumab and recombinant human endostatin, have appeared into the clinic. On the other hand, the molecular organism model can predict the availability of therapy drug and reduce the blind [6,7]. With the higher reliability, EGFR TKI has the advantage in curing the advanced lung adenocarcinoma [8]. Some studies had shown the positive results in the therapeutic alliance

Table 2. The toxic reactions in Chinese elderly patients with advanced lung adenocarcinoma curing by pemetrexed plus carboplatin as an active and tolerable treatment plan.

Toxic reaction (case)	0 grade	I grade	II grade	III grade	IV grade
Hemoglobin	15	5	3	0	0
Leucocyte	9	8	3	2	1
Platelet	16	3	3	1	0
Stomatitis	16	4	3	0	0
Hepatic function	17	4	2	0	0
Nausea and vomiting	13	6	4	0	0
Stomachache and diarrhea	17	3	3	0	0
Constipation	18	3	2	0	0
Peripheral nerve toxicity	17	2	4	0	0

alliance by the cetuximab, bevacizumab and recombinant human endostatin for the advanced lung adenocarcinoma [9]. A step approach for the drug combination is necessary about above-mentioned drug with pemetrexed and carboplatin. Meanwhile, to investigate more predicted index on the base of lung adenocarcinoma undoubtedly improves the effective power and survival benefit by the drug combination of pemetrexed and carboplatin [10].

With the development of age, the disease rate of lung cancer increases year by year. Lung adenocarcinoma possesses an important proportion; most of them can not be healed by operation and only can cure by drug administration. Because the hepatic and kidney function of lung adenocarcinoma patients who do with complication is lower than the health public, the single drug chemotherapy is the standard recommended therapy plan for the old aged lung cancer patients in the most directory [2-5]. However, the standard double drug combination plan is absent nowadays [11]. In the present study, the pemetrexed plus carboplatin was used as an active and tolerable treatment plan in 23 cases that aged more than 70 years with lung adenocarcinoma. It showed that the therapeutic effects were satisfying. The data provided the supporting evidence to use the double drug combination plan in curing the advanced lung adenocarcinoma.

Ten years ago, Elderly Lung Cancer Vinorelbine Italian Study Group (ELCVIS) firstly confirmed the single drug chemotherapy of vinorelbine obviously surpassed the best supporting therapy in the III stage clinical research of the elderly patients with advanced non-small-cell lung cancer (NSCLC) [12]. Later, Gridelli et al. confirmed chemotherapy drug combination with vinorelbine would improve hematotoxicity in the elderly patients with advanced NSCLC [13]. According to the studies, many directories have used the single drug chemotherapy as the first-line therapy plan in elderly patients with lung adenocarcinoma. Recently, Takeda *et al.* confirmed that

the curative effect and living therapeutic review of docetaxel were better than that of the vinorelbine; and the effective power of docetaxel (22.7%) improved 9.9% than the vinorelbine ($p < 0.05$) [14]. Docetaxel was regarded as the standard therapy for the advanced NSCLC. Many studies have pointed that the bone marrow suppression is obvious in the double drug combination plan of vinorelbine plus docetaxel especially the vinorelbine and gemzar could be used to reduce the bone marrow suppression [2-5]. As the new generation anti-lung cancer drug, pemetrexed has the smaller adverse effect of bone marrow suppression in the III stage clinical research than the docetaxel in the patients with NSCLC [15]. On the base of administration, carboplatin would get the better effect. The present study showed that the effective power of the pemetrexed plus carboplatin as an active and tolerable treatment plan in Chinese elderly patients with lung adenocarcinoma was 34.8% that was higher than the single drug administration of docetaxel and vinorelbine as the literature report [16]. Actually, many III stage clinical research of double drug combination plan including the platiniferous drug prompted that the better and younger gerontal patients, can benefit from the double drug combination plan [17,18].

The curative effect of pemetrexed is better than the other type lung cancers [19]. It would perhaps be the one of the reasons for the effective power higher than the others double drug combination plan including the Gridelli plan of vinorelbine plus gemzar [13], in which the OS was 7.0 months. In the present study the RR was 34.8% and OS was 13.7 months. Certainly, we must accept that the case number of our study were smaller than the Gridelli's.

In the present study, 17 cases continuously accepted the chemotherapy after getting the PR/SD, the average chemotherapy was 5.47 cycles. It donates that the patients would accept another 1.47 chemotherapy cycles

after 4 cycles. The argument was residing in whether or not maintenance therapy for NSCLC. Some studies had proved that pemetrexed can prolonged the disease free survival (DFS) and the metabolisms are clear about the active effect in the maintenance therapy for the EGFR-TKI, docetaxel and gemzar [20]. The present study prompted that increasing the chemotherapy cycles would perhaps improve the survival. Regarding to the changing chemotherapy drugs, using the induction chemotherapy drugs processed better direction [21]. However, the cycles and keeping time of the maintenance therapy need a step study.

In conclusion, the chemotherapy drug combination of pemetrexed plus carboplatin as an active and tolerable treatment plan in Chinese elderly patients with lung adenocarcinoma processes the safety, effective power and survival benefit.

5. Conflict of Interest Statement

All authors declare no conflict of interest including financial and personal relationship with other people or organization that could inappropriately influence (bias) the work.

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