Efficacy and Safety of Pemetrexed Combined with Carboplatin in The Treatment Of EGFR-Mutant Advanced NSCLC Patients After First-Line EGFR-TKI Failure

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Abstract

Objective: To investigate the efficacy and safety of pemetrexed combined with carboplatin in the treatment of epidermal growth factor receptor (EGFR)-mutant advanced non-small cell lung cancer (NSCLC) patients after failure of first-line targeted EGFR-tyrosine kinase inhibitor (TKI).

Method: 84 NSCLC patients admitted to xx hospital from March 2017 to March 2019 were involved and divided into the control group (n = 42) and the observation group (n = 42) according to the treatment received. The control group and the observation group were treated with docetaxel combined with carboplatin and pemetrexed combined with carboplatin, respectively. Two to six treatment cycles were applied, until the patient refused to receive further treatment or the disease progressed. After 2 cycles, the two groups were compared in terms of disease remission rates (ORR) and disease control rates (DCR). ELISA was employed to detect serum levels of carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), cytokeratin 19 fragment (CYFRA21-1), and vascular endothelial growth factor (VEGF). The incidences of adverse reactions and survival of patients during the follow-up period were recorded.

Results: ORR and DCR of the observation group were 45.23% and 76.19% ($P<0.05$), respectively, which were higher than those of the control group by 23.81% and 52.38%, respectively. Before treatment, there was no significant difference in serum levels of CEA, CA125, CYFRA21-1 and VEGF between these two group ($P>0.05$). After two treatment cycles, the serum levels of CEA, CA125, CYFRA21-1 and VEGF of patients in both groups were lower than those before treatment, while the serum levels of CEA, CA125, CYFRA21-1 and VEGF of patients in the observation group were lower than those of patients in the control group ($P<0.05$). The incidence rate of adverse reactions in the observation group was lower than that in the control group ($P<0.05$). As of March 2020, 60 of the 84 NSCLC patients died. The mortality of the observation group was 61.90% (26/42), which was lower than that of the control group (80.95%, 34/42). The median survival time of the observation group was 27 months, which was higher than that of the control group by 16 months ($P<0.05$).

Conclusions: The combination of pemetrexed and carboplatin in the treatment of NSCLC exhibits an excellent effect as it can significantly reduce the serum levels of tumor markers and adverse reactions. Characterized by high safety and effectively prolonged patient survival, this treatment is worthy of promotion and application.

Keywords: non-small cell lung cancer (NSCLC); pemetrexed; carboplatin; epidermal growth factor receptor

1. Introduction

Lung cancer is a common, relatively high incidence malignant tumour with a mortality rate [1]. Non-small cell lung (NSCLC) has a fairly insidious onset as one of the most common pathologic classifications of lung cancer, and optimal times of operation have normally passed before diagnosis, which prevents the elimination of

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surgerical procedures. NSCLC is currently mainly treated for chemotherapy or targeted treatment [2, 3]. As a primary treatment for advanced EGFR NSCLC, the targeted tyrosine kinase tyrosine (TKI) epidermal growth factor receptor has been used to date. When the treatment with EGFR-TKI does not manage the disease [3, 5] chemotherapy remains the most effective therapeutic option. In this study we suggest treating patients with advanced EGFR-mutant NSCLC in combination with pemetrexed and carboplatin following firstline failures of the EGFR-TKI and to investigate their efficacy and safety.

2. Data and method
2.1 General

Subjects were selected from 84 patients with EGFR-mutant advanced NSCLC after first-line EGFR-TKI failure admitted to our hospital from March 2017 to March 2019. There were 49 males and 35 males whose age was 37~69-year-old, with the average being 50.17±7.37.

Inclusion criteria:
1) Diagnosed after pathological examination;
2) Subjected to disease progression after first-line EGFR-TKI therapies;
3) At stage Ⅲ or Ⅳ per TNM classification;
4) EGFR-mutant positive indicated by genetic testing;
5) With a ≥3-month estimated time of survival.

Exclusion criteria:
1) With damaged organs including heart and liver;
2) Combined with other malignant tumors;

3) Combined with mental disorders;
4) With allergic history towards pemetrexed, docetaxel or carboplatin.

According to the treatment method, patients were divided into the control group (n = 42) and the observation group (n = 42) whose differences in patient age, gender and other general clinical data were statistically insignificant (*P*>0.05).

2.2 Treatment

Control group: docetaxel-carboplatin mixture. The intravenous infusion was used to dissolve docetaxel (75 mg / m2) in 100 ml of physiological Saline within 1 hour. Carboplatin AUC = 5 per day. Pemetrexed in combination with carboplatin the observation group: Pemetrexed (500 mg / m2) has been dissolved in 150 mL of intravenous infusion in physiological saline. Carboxylic AUC = 5 / fold. From 1 week before infusion to the three weeks after treatment foliar acid, 400 µg / d, was administered.

Vitamin B$_{12}$ was given intramuscularly every 3 treatment cycles until three weeks after the treatment. Patients from both groups were given dexamethasone tablets (8 mg/time, 2 times/d, three days) starting from the day before infusion. A total of two to six treatment cycles were conducted and each treatment cycle lasts for 21 d. Treatment was discontinued if patients refused to be further treated or the disease progressed.

2.3 Indicators
2.3.1 Observation of short-term efficacy

After two treatment cycles, their clinical effects on patients were evaluated (Table 1).

Table 1. **Evaluation criteria for the treatment's clinical effects on patients**

Effect	Standards
Progressive disease	Lesion grew by ≥20%, or new lesions occurred
Stable disease	Lesion grew by < 20%, or lesion reduced by <30% with a ≥4-week duration
Partial remission	lesion reduced by ≥30% with a ≥4-week duration
Complete remission	Lesion disappeared completely with a ≥4-week duration
Disease remission rate	(PR+CR) /42×100%
Disease control rate	(SD+PR+CR) /42×100%

2.3.2 Detection of tumor markers in serum

Pacient enzyme-like immuno-sourcing test (ELISA) were measured before, after two therapeutic cycles at serum concentrated levels of carcino-embryonic antigen (CEA), carbohydrate antigen 125 (CA125), cytokeratin 19 fragment

(CYFRA21-1) and vascular endothelial growth factor (VEGF).

2.3.3 Unfavorable effects

During the follow-up period, patients in both groups were counted for adverse reactions such as

anaemia, diarrhoea, nausea and vomiting, thrombocytopenia, Leukopenia, abnormal liver and renal functions, etc.

2.3.4 The period of follow-up

After the end of the cycles of radiotherapy, follow up visits were carried out through telephone calls or regular inspections to determine the overall survival rate or patients refusing further treatment. In March 2020 the monitoring was completed.

2.4 Statistical method

The SPSS22.0 software was used for data processing. Measurement data were represented as mean ± standard deviation ($\bar{x}$ ±s), and independent t tests were conducted for pairwise comparisons between two groups. Enumeration

data were represented as frequency and percentage [n (%)], for which χ^2 tests were applied. The relationship between the different chemotherapies administered to NSCLC patients and their survival time was analyzed via the Kaplan-Meier survival curve, and Log-rank tests were used for comparisons. The test level was set as $\alpha = 0.05$, and $P<0.05$ indicates a statistically significant difference.

3. Results
3.1 Comparison of short-term efficacies

ORR and DCR of the observation group were 45.23% and 76.19%, respectively, which were higher than those of the control group by 23.81% and 52.38%, respectively ($P<0.05$), as shown in Table 2.

Table 2. **Comparison of short-term efficacies (n, %)**

	Cases	PD	SD	PR	CR	ORR	DCR
control group	42	20 (47.62)	12 (28.57)	10 (23.81)	0 (0.00)	23.81 (10/42)	52.38 (22/42)
observation group	42	10 (23.81)	13 (30.95)	19 (45.23)	0 (0.00)	45.23 (19/42)	76.19 (32/42)
χ^2						4.266	5.185
P						0.039	0.023

3.2 Tumor markers in serum

The differences between the two groups were statistically insignificant (P>0.05), in terms of serum CEA, Ca125, CYFRA21-1, and VEGF prior to treatment. CA125, CYFRA21-1 and VEGF were all

lower than the pre-treatment levels following two treatment cycles. In addition, CEA, CA125, CYFRA21-1, and VEGF serum levels were significantly lower than those shown in Table 3 for patients in the control group (P<0.05).

Table 3. **Comparison of tumor markers in serum (n, $\bar{x}$ ±s)**

Group	Time	CEA (ng/mL)	CA125 (U/mL)	CYFRA21-1 (ng/mL)	VEGF (pg/mL)
control group (n = 42)	Before treatment	13.21±2.45	95.87±12.79	15.55±2.63	140.75±20.79
	After 2 treatment cycles	8.74±1.46*	74.55±9.24*	12.34±1.78*	100.21±15.68*
the observation group (n = 42)	Before treatment	13.55±1.59	97.16±11.93	14.97±2.58	137.58±18.74
	After 2 treatment cycles	6.82±1.27*#	63.72±8.17*#	10.07±1.37*#	70.41±10.78*#

p.s.: compared with the same group before treatment, *$P<0.05$; compared with the control group after 2 treatment cycles, #$P<0.05$.

3.3 Incidence of adverse reactions

The incidence rates of adverse reactions (e.g., anemia, diarrhea, nausea and vomiting, thrombocytopenia, leukopenia, abnormal liver and kidney functions) in the observation group were lower than the control group ($P<0.05$), as shown in Table 4.

3.4 Survival time

60 of 84 NSCLC patient deaths were reported in March 2020. Observation group mortality was 61.90% (26/42), less than the control group mortality was 80.95% by 34/42). The median observation group's duration of survival was 27 months, which was 16 months higher than the control group (P<0.05), as shown by Figure. 1.

Table 4. **adverse reactions (n, %)**

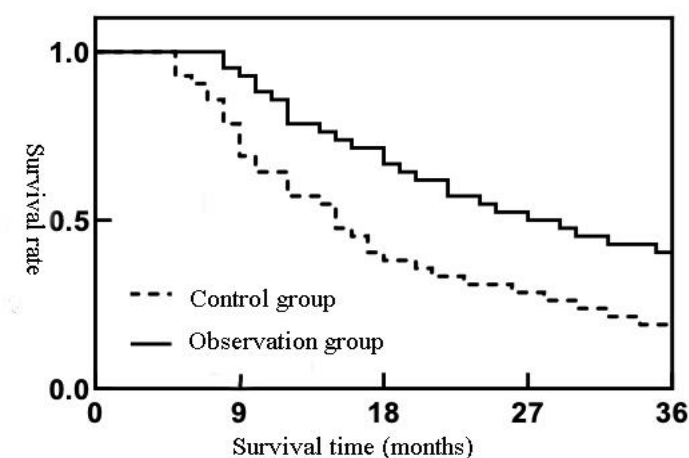|	Anemia	Diarrhea	Nausea and vomiting	Thrombocytopenia	Leukopenia	Abnormal liver and kidney functions
Control group (n = 42)	27 (64.29)	20 (47.62)	26 (61.90)	10 (23.81)	13 (30.95)	8 (19.05)
Observation group (n = 42)	12 (28.57	15 (35.71)	14 (33.33)	3 (7.14)	5 (11.90)	2 (4.76)
χ^2	10.769	1.225	6.873	4.459	4.525	4.087
P	0.001	0.268	0.009	0.035	0.033	0.043

Figure 1. **survival time**

4. Discussion

No obvious symptoms can be seen at the early stage of the NSCLC, but they can quickly deteriorate. Very often, by the time the diagnosis is made, the disease has already progressed to an advanced stage, when the surgical eradication becomes insignificant for the survival of the patient. EGFR is a transmembrane glycoprotein that plays an important role in signal transduction and its mutation has a significant impact on tumour cell proliferation [7]. EGFR-TKI therapy is the primary method for the treatment of EGFR-mutant NSCLC. However, due to significant individual differences, some patients suffer from drug resistance following high-dose medication, resulting in decreased drug sensitivity [8,9]. Effective and reliable treatment is therefore urgently needed for patients with EGFR-mutant advanced NSCLC following first-line EGFR-TKI failure.

Combination therapies of pemetrexed, gemcitabine, vinorelbine, docetaxel with platinum drugs are popular therapeutic options for patients with EGFR-mutant advanced NSCLC after first-line

EGFR-TKI failure [10, 11]. As a platinum drug, carboplatin can reduce therapeutic side-effects, minimizing gastrointestinal irritation and hepatorenal damages [12]. Single-use of platinum drugs has huge limitations and poor efficacy. Hence, dual-use of chemotherapies is often applied in the clinic to enhance their efficacies and reduce the incidence rate of drug resistance [13]. Docetaxel is a potent anti-tumor drug that destroys the microtubule and microfilament structures of cells, thus inhibiting cell division and stalling cells in the M phase, which is effective mainly against proliferating cells [14]. However, pemetrexed with less toxicity and side-effects is often suggested in place of docetaxel, because docetaxel is only effective against proliferating cells and has greater toxicity and side-effects. Via the enzymes in the metabolic pathways that rely on folic acids such as thymidylate synthase (TS) and dihydrofolate reductase (DHFR), pemetrexed stalls tumor cells in the S phase, thus exerting its anti-tumor effects [16, 17].

Compared with combination of docetaxel and

carboplatin, combination of pemetrexed and carboplatin can improve therapeutic ORR and DCR, significantly reduce patients' serum levels of CEA, CA125, CYFRA21-1 and VEGF, and lower the incidence rate of adverse reactions. The results indicate that combination of pemetrexed and carboplatin is efficacious against NSCLC, and it reduced the serum levels of tumor markers, alleviating the gastrointestinal and the myelosuppressive effects of patients with EGFR-mutant NSCLC. One plausible explanation is that pemetrexed has a rather long half-life that allows a longer time for the drug to stay and interact in tumor cells, thus boosting its efficacy while reducing the incidence rate of adverse reactions [18]. It is further proved that the search for chemotherapy drugs that can affect tumor cell cycles is of great significance for improving patient tolerance and reducing adverse reactions [19].

As of March 2020, 60 of the 84 NSCLC patients died. The mortality of the observation group was 61.90% (26/42), which was lower than that of the control group (80.95%, 34/42). The median survival time of the observation group was 27 months, which was higher than that of the control group by 16 months ($P<0.05$). The results demonstrate that treatment by pemetrexed combined with carboplatin can effectively control the progression of NSCLC and prolong the survival time of patients. It is possibly due to the fact that pemetrexed can inhibit tumor cell proliferation, thus inhibiting tumor growth and stalling tumor evolutional process [20]. Additionally, pemetrexed can participate in tumor evolution by affecting the expression of tumor cells in patients' blood circulations [21].

5. Conclusions

The combination of pemetrexed and carboplatin in the treatment of NSCLC exhibits an excellent effect as it can significantly reduce the serum levels of tumor markers and adverse reactions. Characterized by high safety and effectively prolonged patient survival, this treatment is worthy of promotion and application.

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