

Original Research Article

Efficacy and safety of combined use of docetaxel-gemcitabine chemotherapy and 5-fluorouracil targeted therapy in the treatment of advanced non-small cell lung cancer

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Abstract

Purpose: To determine the efficacy of combined use of docetaxel-gemcitabine chemotherapy and 5-fluorouracil (5-FU) targeted therapy for the treatment of advanced non-small cell lung cancer (NSCLC).

Methods: Eighty advanced NSCLC patients in Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University) (March 2020 - March 2021) were selected and randomly assigned to chemo group (CHEG) and combination group (COMG), with 40 patients per group. All patients received docetaxel-gemcitabine chemotherapy. On the 1st, 8th and 15th day of treatment, docetaxel (20 mg/m²) was injected via intravenous drip. On the 2nd, 9th and 16th day, gemcitabine hydrochloride (1 g/m²) was injected, also via intravenous drip. The dose regimens were repeated once every 28 days. In addition, patients in COMG received 5-FU targeted therapy at a dose of 15 mg/kg body weight, in 5 % glucose solution, via intravenous drip for 5 - 8 h daily for 5 consecutive days. Thereafter, the dose was reduced by half and the drug injected once every other day. Therapeutic efficacy as well as various clinical and biochemical indices were assessed in both groups.

Results: Compared with CHEG, COMG had a slightly higher objective remission rate and a higher disease control rate ($p < 0.05$). After treatment, there was decrease in levels of serum carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC) and cytokeratin 19 fragment antigen 21-1 (CY-FRA21-1), with lower levels in COMG than in CHEG ($p < 0.05$). The median survival time was shorter in CHEG than in COMG ($p < 0.05$). However, no notable differences in the incidence of adverse reactions were observed between the two groups ($p > 0.05$).

Conclusion: Combined use of docetaxel-gemcitabine chemotherapy and 5-FU-targeted therapy down-regulates the expressions of serum CEA, SCC and CY-FRA21-1 tumor markers, but significantly prolongs overall survival of patients. Therefore, this therapeutic strategy is safe but should be subjected to further clinical trials prior to application in clinical practice.

Keywords: 5-Fluorouracil (5-FU), Advanced non-small cell lung cancer (NSCLC), docetaxel; Gemcitabine

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INTRODUCTION

Lung cancer is a malignant tumor threatening the health of people worldwide. In addition, non-small cell lung cancer (NSCLC) is a predominant type which accounts for approximately 80-85% of lung cancer cases. NSCLC is reported to be associated with very high mortality, mainly because of absence of obvious symptoms at the early stage of the disease. Thus, approximately 75% of patients are diagnosed at the middle and advanced stages of NSCLC. The main treatment strategies used for advanced NSCLC are radiotherapy and chemotherapy. However, the patients may suffer from intolerable adverse reactions without adjuvant therapy [1-4]. Recently, new and efficient anti-tumor drugs such as docetaxel and gemcitabine were developed, and some researchers have reported the clinical efficacy of combined use of the two drugs [5, 6]. With advancements in molecular biology, targeted drug therapy has been gradually promoted in the treatment of NSCLC, with improved clinical results.

5-Fluorouracil (5-FU), an anti-pyrimidine drug that is enzymatically converted to 5-fluorodeoxyuracil nucleotide, exerts its antitumor effect by inhibiting the synthesis of DNA via inhibition of thymine nucleotide synthetase [7-10]. Due to limited reports on 5-FU-targeted therapy for NSCLC, this research was carried out for determining the effects of combination of docetaxel-gemcitabine chemotherapy with 5-FU targeted for advanced NSCLC.

Subjects and grouping

Eighty (80) patients with advanced NSCLC treated in Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University) (March 2020 - March 2021) were enrolled. Forty (40) advanced NSCLC patients were assigned to the chemo group (CHEG), while the other 40 patients formed the combined group (COMG). The study received the approval and supervision of the ethics committee of Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University (approval no. 20200112), and followed the guidelines of the Declaration of Helsinki, as revised in 2013 [11]. The patients and their family members signed informed consent forms.

Inclusion criteria

The enrolled patients included those who were diagnosed with stage IIIB or IV NSCLC after pathological examination, patients aged \geq 55 years, subjects with at least one measurable

lesion on CT scan consistent with the diagnosis criteria of the World Health Organization (WHO), patients who did not receive chemotherapy or targeted therapy prior to the study, and those without contraindications for chemotherapy and the targeted drug used. In addition, patients with the expected survival time $>$ 6 months, and those with ECOG performance status scores of 0-2 points were also admitted.

Exclusion criteria

Patients with cardiovascular and cerebrovascular diseases, those who suffered from severe hepatic and kidney dysfunction or other malignant tumors; those who could not cooperate with the researchers, and patients with uncontrollable nerve metastasis, were excluded from the study.

Treatments

Chemo group (CHEG)

Prior to chemotherapy, anti-allergy pretreatment was carried out. On the 1st, 8th and 15th days of treatment, docetaxel injection (specification: 20 mg; Rhone-Poulenc Rorer S.A.; approval no. X20010340) was given via intravenous drip at a dose of 20 mg/m². On the 2nd, 9th and 16th days, gemcitabine hydrochloride injection (0.2 g; Jiangsu Hansoh Pharmaceutical Group Co. Ltd; NMPA approval no. H20030104) was administered at a dose of 1 g/m² via intravenous drip, and the dose regimen was repeated once every 28 days. During chemotherapy, conventional symptomatic and supportive treatments were given. The hemogram of each patient was checked once or twice weekly. At the start of each cycle, the hemogram and hepatic and kidney functions were rechecked before medication, and the next cycle of chemotherapy was started if each indicator was within the normal range, otherwise, drug administration was delayed [12].

Combination group (COMG)

5-Fluorouracil (5-FU, Nantong Haiers Pharmaceutical Co. Ltd; NMPA approval no. H20057518) was dissolved in 5 % glucose solution and intravenously dripped daily at 15 mg/kg body weight lasting 5 - 8 h for 5 consecutive days. Thereafter, the dose was reduced by half, and the drug was injected once every other day until there were neurotoxic effects. The treatment with docetaxel-gemcitabine chemotherapy was same as in CHEG.

Evaluation of parameters/indices

General profiles of patients

Patient's age, duration of disease, gender, clinical stage, tissue type, ECOG score, body weight, smoking history, drinking history and other general information were recorded and processed statistically.

Clinical efficacy of treatment

Clinical efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) established by WHO [13]. In this evaluation, clinical efficacy was classified as complete response, partial response, stable disease and progressive disease. *Complete response* referred to complete disappearance of tumors for over one month, while *partial response* referred to > 50% increase in the product of the maximum diameter and maximum vertical diameter of the tumor, without deterioration of the lesions for over one month. In contrast, *stable disease* referred to ≤ 50% decrease or ≤ 25% increase in the product of the maximum diameter and maximum vertical diameter of the tumor for over one month, while *progressive disease* referred to > 25% increase in the product of the maximum diameter and maximum vertical diameter of the tumor. The objective response rate (ORR) and disease control rate (DCR) were calculated using Eqs 1 and 2, respectively.

$$ORR = \frac{(CR + PR)}{T} \times 100 \dots\dots\dots (1)$$

$$DCR = \frac{[(CR + PR + SD)]}{T} \times 100 \dots\dots\dots (2)$$

where ORR = objective response rate; DCR = disease control rate; CR = number of patients with complete response; PR = number of patients with partial response; SD = number of patients with stable disease; T = total number of patients.

Serum indicators

Fasting venous blood (5 mL) was drawn from each patient in the morning, and serum was obtained after centrifugation of the blood at 3,000 rpm for 10 min. Serum levels of carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC) antigen and cytokeratin 19 fragment antigen 21-1 (CYFRA21-1) were determined using enzyme-linked immunosorbent assay (ELISA) kits. The normal reference values for CEA, SCC and CY-FRA21-1 were < 5.90 µg/L, < 1.5 ng/mL, and < 3.3 ng/mL, respectively.

Survival time

The survival curves of patients in both groups were drawn after recording their death time *via* telephone or clinic follow-up.

Adverse reactions

The incidence of adverse reactions in patients during treatment was evaluated based on NCI-CTC 3.0 criteria.

Statistical analysis

In this study, data were analyzed with SPSS21.0 software, while graphics were done with GraphPad Prism 7 software (GraphPad Software, San Diego, USA). The results comprised enumeration data and measurement data which are expressed as n (%) and mean ± SD, respectively, and were analysed using χ^2 test and *t*-test, respectively. Differences were considered statistically significant at $p < 0.05$.

RESULTS

General profiles of patients

No statistical differences in patients' general profile were shown between the two groups ($p > 0.05$, Table 1).

Clinical treatment efficacy

Although the ORR was higher in COMG than in CHEG, no obvious differences were shown between the two groups ($\chi^2 = 2.0513$, $p = 0.152$), with higher DCR in COMG than in CHEG ($\chi^2 = 4.7127$, $p = 0.030$). These data are shown in Figure 1.

Serum indicators

After treatment, serum levels of CEA, SCC and CY-FRA21-1 in patients were lower than the corresponding pre-treatment values, but they were lower in COMG than in CHEG ($p < 0.05$; Table 2).

Survival time of patients

Figure 2 indicates shorter median survival time in CHEG (10 months) than in COMG (19 months; $\chi^2 = 4.6768$, $p = 0.031$).

Incidence of adverse reactions

During treatment, patients in both groups suffered adverse reactions such as fatigue, poor appetite, nausea, rash and hematological

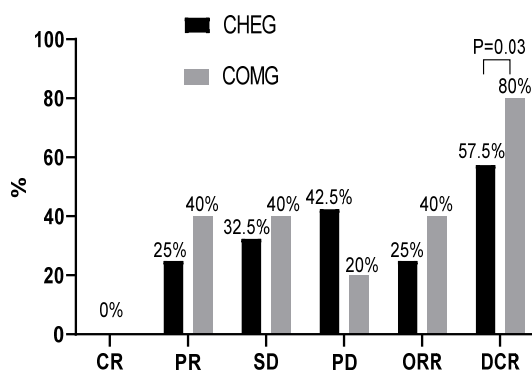
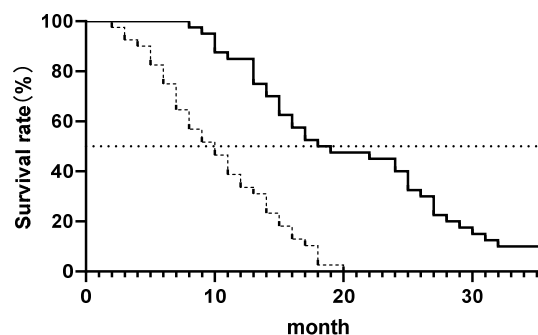
Table 1: Comparison of general profiles (n = 40)

Indicator	CHEG	COMG	χ^2/t	P-value
Age (years)	84.17±4.56	83.81±4.29	0.3637	0.7171
Duration of disease (months)	5.84±1.23	6.05±1.28	0.7482	0.4566
BMI (kg/m ²)	24.65±2.83	23.77±2.58	1.4533	0.1501
Male/female	29/11	26/14	0.5236	0.469
Clinical stage			0.0508	0.822
IIIB	18 (45)	17 (42.5)		
IV	22 (55)	23 (57.5)		
Tissue type			0.2198	0.639
Squamous cell carcinoma	20 (50)	19 (47.5)		
Adenocarcinoma	13 (32.5)	15 (37.5)		
Large cell carcinoma	7 (17.5)	6 (15)		
ECOG score			0.3463	0.556
0 point	1 (2.5)	2 (5)		
1 point	32 (80)	32 (80)		
2 points	7 (17.5)	6 (15)		
Weight loss more than 5%	34 (85)	32 (80)	0.3463	0.556
Smoking history	31 (77.5)	30 (75)	0.0690	0.793
Drinking history	29 (72.5)	31 (77.5)	0.2667	0.606

Table 2: Comparison of serum levels of indicators (ng/ml, $\bar{x} \pm s$)

Indicator		CHEG	COMG	t	P-value
CEA	Before treatment	28.13±8.54	26.96±9.13	7.6356	< 0.001
	After treatment	22.07±9.18	10.49±2.78		
SCC	Before treatment	2.65±1.04	2.59±1.06	4.1950	0.0001
	After treatment	2.46±0.97	1.73±0.52		
CY-FRA21-1	Before treatment	5.86±2.67	5.93±3.59	2.1476	0.0348
	After treatment	3.85±1.27	3.18±1.51		

toxicity, but the between-group differences were not significant ($p > 0.05$; Table 3).

**Figure 1:** Comparison of clinical treatment efficacy**Figure 2:** Comparison of the survival times. **Note:** Continuous line represents COMG, while dashed line represent CHEG**Table 3:** Comparison of incidence of adverse reactions [n (%)]

Adverse reaction	CHEG	COMG	χ^2	P-value
Fatigue	15 (37.5)	14 (35)	0.0541	0.816
Poor appetite	33 (82.5)	31 (77.5)	0.3125	0.576
Rash	12 (30)	15 (37.5)	0.5031	0.478
Nausea	28 (70)	26 (65)	0.2279	0.633
Hematological toxicity	13 (32.5)	14 (35)	0.0559	0.813

DISCUSSION

Changes in people's diets and lifestyles in recent times have led to increased risks of various respiratory diseases. For example, lung cancer is caused mainly by smoking and environmental pollution, and its incidence rises with increase in age [14]. Non-small cell lung cancer (NSCLC) is a prevalent pathological type of lung cancer in which tumor tissues split and spread slowly. Since the clinical symptoms are not obvious at the early stage, most NSCLC cases are diagnosed at the middle and advanced stages of the disease, leading to a high fatality rate. Since most patients have already missed the best period for surgery before they visit the hospital, conventional radiotherapy and chemotherapy are mostly applied to control the tumor.

It has been reported that the efficacy associated with the use of only docetaxel or gemcitabine for treating advanced NSCLC was similar, or even superior to that of conventional platinum-based regimens [15]. Moreover, it was shown that combination of docetaxel and gemcitabine not only produced a synergistic effect but also reduced the dose of a single drug and alleviated the toxic side effects of drugs and drug dependence [15]. However, radiotherapy and chemotherapy cause obvious adverse reactions in patients and even damage normal cells, thereby triggering other diseases. Therefore, clinical research is mainly focused on evolving effective and comprehensive regimens for improving treatment efficacy and alleviating adverse reactions.

With recent advancements in molecular biology, targeted therapy has become a novel treatment strategy for cancer. It is a more specific intervention which reduces damage to normal cells, when compared to conventional radiotherapy and chemotherapy. 5-Fluorouracil (5-FU), a pyrimidine fluoride, belongs to the class of antimetabolic and antineoplastic drugs which inhibit thymidylate synthase and block the conversion of deoxypyrimidine nucleotides to thymine nucleotides, thereby interfering with DNA synthesis. Moreover, 5-FU exerts inhibitory effect on RNA. In clinics, 5-FU is adopted for adjuvant treatment of gastrointestinal tumors and breast cancer surgery, and as palliative treatment of some non-surgical malignancies of the gastrointestinal tract, breast, and liver [16]. At present, not much is known about the efficacy of 5-FU in dealing with advanced NSCLC.

Although the ORR in COMG was higher than that of CHEG, no obvious difference was shown

between COMG and CHEG. However, the DCR was markedly higher in COMG. Thus, compared with single chemotherapy, the combination of chemotherapy regimen of docetaxel-gemcitabine with 5-FU targeted therapy significantly enhanced clinical treatment efficacy in advanced NSCLC patients. This finding conforms with the conclusion obtained in other references [17,18].

After treatment, the serum levels of CEA, SCC and CY-FRA21-1 in NSCLC patients were lower than the corresponding pre-treatment values. However, these indicators were lower in COMG than in CHEG, suggesting that the combined therapy markedly inhibited the expressions of the tumor markers CEA, SCC and CY-FRA21-1. The median survival times of CHEG and COMG were 10 and 19 months, indicating that the combined therapy effectively prolonged the overall survival of advanced NSCLC patients. During treatment, patients in both groups suffered adverse reactions comprising fatigue, poor appetite, nausea, rash, and hematological toxicity, but no remarkable differences were shown between the two groups.

These results indicate that 5-FU-targeted therapy was safe and feasible, without exacerbating the adverse reactions of chemotherapy. In clinical practice, the doses of 5-FU, docetaxel and gemcitabine can be scientifically adjusted in relation to the patients' conditions. The drug 5-FU is a specific agent which exerts the strongest tumor cell-killing effect at the DNA synthesis phase. It exhibits time-dependent manner in killing tumor cells. The combined use of 5-FU and docetaxel-gemcitabine significantly enhanced the chemotherapeutic effect on advanced NSCLC

Limitations of the study

Due to the limited research funds, time, and accuracy of the investigation, only 80 patients with advanced NSCLC were selected for the study. Therefore, the efficacy of the combined therapy should be further investigated using expanded studies with a larger sample size.

CONCLUSION

The combination of docetaxel-gemcitabine chemotherapy with 5-FU targeted therapy improves clinical efficacy in advanced NSCLC patients, down-regulates the expressions of serum CEA, SCC and CY-FRA21-1 in patients, and prolongs patients' overall survival. Thus, the combined treatment has therapeutic benefits, but the further clinical trials should be carried out prior to clinical trials.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yeyu Qi conceived and designed the study, and drafted the manuscript. Jing Xie collected, analyzed and interpreted the experimental data. Haixia Wang revised the manuscript for important intellectual contents. All authors read and approved the final manuscript. Yeyu Qin and Jing Xie contributed equally to this work.

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