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Comparative effectiveness study of single high-dose cisplatin with fractionated doses cisplatin in first-line therapy for treatment-naive Chinese patients with advanced non–small-cell lung cancer

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ABSTRACT

Background: Cisplatin is one of the most effective chemotherapeutic drugs for patients with advanced non–small-cell lung cancer (NSCLC). Single high-dose cisplatin is a commonly used chemotherapy regimen in the world. At present, fractionated doses cisplatin is used in most hospitals in China. Although many doctors have begun to try a single dose of cisplatin, there are still few studies on the comparison of the 2 regimens. This study describes the efficacy and side effects of cisplatin single-dose administration and fractionated doses regimen in the treatment of advanced NSCLC.

Methods: A retrospective study was conducted on 219 patients with advanced NSCLC who received chemotherapy

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with DDP were divided into 2 groups according to the single dose of cisplatin from January 2014 to December 2017. For experimental group, 108 patients were enrolled and received DDP at a dose of 75 mg/m^2 on day 1. A total of 111 patients were enrolled in the control group, and DDP was administrated at 25 mg/m^2 on days 1-3. The efficacy, toxicity, and progression-free survival of the 2 groups were observed and analyzed.

Results: In the experimental group, the numbers of patients who received PR, SD, and PD were 66, 34, and 8 respectively. In the control group, the numbers of patients who received PR, SD, and PD were 18, 77, and 16 respectively. The percentages of patients with a objective response rate response in the experimental group were significantly higher than that in the control group (61.11% vs 16.22%, $P < 0.0001$). The incidence of III-IV vomiting in the experimental group was lower than that in the control group (11.11% vs 26.13%). The incidence of I-II hiccups in the experimental group was higher than that in the control group (15.74% vs 10.81%). None of the patients had III-IV degree nephrotoxicity. Myelosuppression mainly manifested as leukopenia. In the experimental group, the incidence of I-II degree of leukopenia was 71.30%, and the III-IV degree was 7.41%, which was 74.77% and 11.71 respectively in the control group. A small number of patients have a decrease in mild platelets and hemoglobin.

Conclusion: For patients with advanced NSCLC who require chemotherapy with DDP regimen, the short-term effect of single-dose administration of DDP is better than that of fractional small-dose administration. Toxicity can be tolerated and it is worth promoting clinically.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide,[1] and is the most common type of cancer in China, accounting for 21.3% of new cancer cases in 2012.[2] Among patients with lung cancer, approximately 85% are non–small-cell lung cancer (NSCLC).[3] With improvement in diagnosis and treatment, the prognosis of lung cancer remains poor. The 5-year survival rate of NSCLC was lower than 15%.[1]

Treatments for lung cancer patients mainly include surgery, chemotherapy, radiotherapy, target therapy, and immunotherapy in recent years.[4,5] Most of the patients are in advanced stage when diagnosed, therefore lost the chance of surgery.[6] With the development of targeted therapy and immunotherapy,[5,7,8] many new drugs have also come out, but platinum-based the combination chemotherapy remains one of the most effective methods for the treatment of NSCLC.[8,9] However, there is no uniform standard for the optimal dose and method of administration for cisplatin (DDP) applications.[10,11] Clinical studies of different methods of DDP application were derived empirically[12] in china.

The methods of DDP application for Chinese patients with advanced NSCLC are insufficient. Fractionated doses cisplatin is used in most hospitals in China. There are few studies on the comparison of efficacy and toxicity between cisplatin single-dose administration and fractionated doses regimen. In order to explore more reasonable application, to improve clinical efficacy and reduce adverse reaction, this retrospective study collected and evaluated the short-term efficacy, progression-free survival (PFS), and side effects of different methods of DDP application in Chinese advanced NSCLC patients.

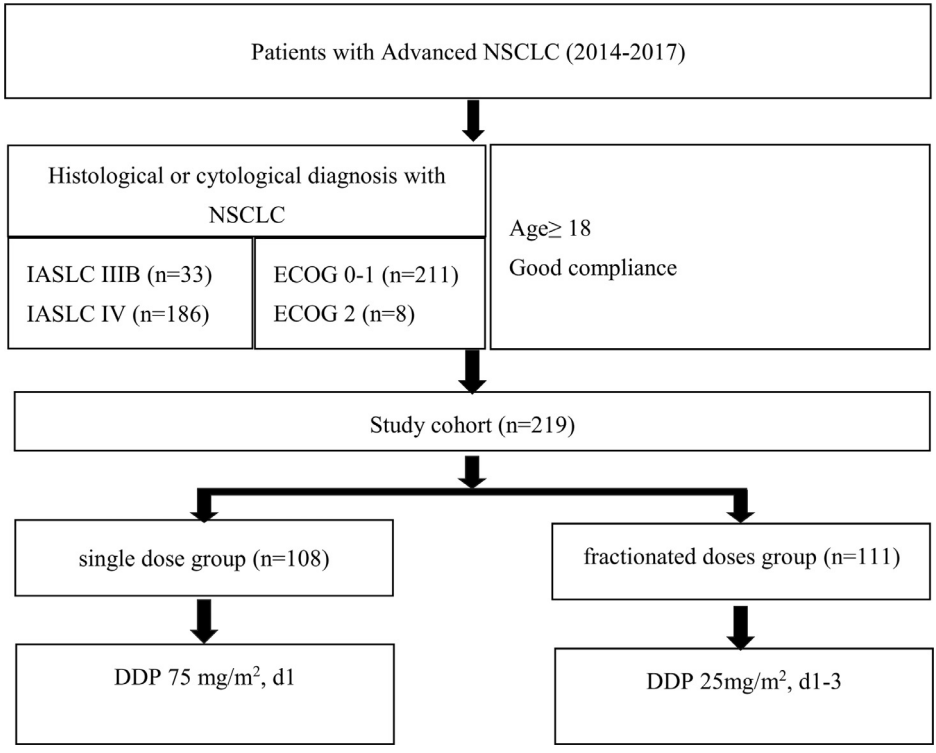

Fig. 1. Flowchart of this retrospective study design.

Patients and methods

Patient enrollment

The study was conducted at department of medical oncology, Jiangsu Cancer Hospital, Nanjing, PR China, which was approved by the Research Ethics Committee on human research 38 of Jiangsu Cancer Hospital. A total of 219 patients with advanced NSCLC enrolled to our research from January 2014 to December 2017 were retrospectively divided into 2 groups according to the method of DDP use. In the experimental group (single dose group), DDP was administered at a dose of 75 mg/m^2 on day 1, and in the control group (fractionated doses group) DDP was given in 3 days (d1-3). Among them, 108 patients in the experimental group and 111 patients in the control group aged 18-70 years. All patients were diagnosed as NSCLC by pathology or cytology, in stage IIIB-IV according to the TNM staging criteria established by the International Union Against Cancer (UICC) in 2009. Each patient had a measurable but inoperable lesion, and all patients had normal liver, kidney function, blood routine, and cardiopulmonary function before treatment; all cases had an ECOG score of less than 2 points and a predicted survival period of more than 3 months without chemotherapy contraindications. Blood routine was measured every 3-4 days after chemotherapy, while liver and kidney function was measured once a week. There were 82 patients with adenocarcinoma and 26 patients with squamous cell carcinoma in the experimental group, 79 patients with adenocarcinoma and 32 patients with squamous cell carcinoma in control group. There were 29 females and 79 males in the experimental group, and 35 females and 76 males in the control group. The flowchart and analysis cohorts are presented in Fig. 1. The exclusion criteria for patients were those who had not follow-up less than 6 cycles

from the initial chemotherapy. All the data were collected until the progression of the tumor, death, or last medical fellow-up.

Study design

The primary effectiveness endpoint, PFS, is defined as the time from the initiation of treatment to objective tumor progression or death. The response data included the total response (CR), partial response (PR), stability disease (SD), and progressive disease (PD), according to response evaluation criteria in solid tumors (RECIST, 1.1).[13] Objective response rate (ORR) is considered as CR+ PR. Safety outcomes are measured by the proportion or incidence of adverse events (AE), which were evaluated according to the National Cancer Institute–Common Toxicity Criteria for Adverse Events (NCI-CTCAE, version 4.03).

Treatment received

All the patients were treated with cisplatin-based combined chemotherapy. Cisplatin was a product of Qilu Pharmaceutical Co., Ltd. According to the DDP dosing regimen, 219 patients were divided into the experimental group (DDP 75 mg/m^2, d1) and the control group (DDP 25mg/m^2, d1-3). Twenty-one days were 1 cycle in both groups. Other chemotherapy drugs in the protocol are mild vomiting risk drugs. Different drugs are selected according to different pathological types, including pemetrexed, docetaxel, and paclitaxel, which were administered on the first day of chemotherapy. All adenocarcinoma patients used pemetrexed (500 mg/m^2, d1) in the 2 groups. In the experimental group, 4 patients used docetaxel (75 mg/m^2, d1) and 5 patients used paclitaxel (175 mg/m^2, d1). In the control group 12 patients used docetaxel (75 mg/m^2, d1) and 20 patients used paclitaxel (175 mg/m^2, d1). Adverse reactions were observed every cycle, and efficacy was evaluated after 2 cycles. Both groups received palonosetron plus dexamethasone before chemotherapy, and oral aprepitant capsules for antiemetic treatment; if III/IV degree myelosuppression occurred, rhG-CSF was used for treatment. The experimental group was given a large amount of rehydration hydration, in which the first day of intravenous infusion reached 3000 ml, the next day reached 2500 ml, and the third day reached 2000 ml. The patients were asked to drink more water. Moreover mannitol and cefuroxime sammy were used to reduce the nephrotoxicity of cisplatin. Twenty-four hour urine volume was recorded for 3 consecutive days. Cisplatin was dissolved in 500 ml 0.9% saline, protected from light, and finished in 2-3h. For all stage IV adenocarcinoma patients, if the treatment were effective, it would continue to 4-6 cycles, followed by pemetrexed maintain treatment until the disease progressed. For all stage IIIB patients, they received radiation after 4-6 cycles chemotherapy.

Data collection

Patients' data, including the chief complaint, disease history, physical examination, imaging examinations, and biochemical laboratory tests, were collected at our cancer hospital, as the time from initial enrolment and subsequently at least 4 cycles treatment, until disease progression, death or study cutoff.

Statistical analysis

Statistical analysis was performed after the completion of data collection and verification. Full patient demographic information and baseline characteristics were tabulated and analyzed by treatment groups. Chi-Square Test or Fisher Exact Test was used to examine the difference of

Table 1
Baseline characteristics of the patients.

Characteristic	Single high-dose DDP (n = 108) No. (%)	Fractionated doses DDP (n = 111) No. (%)	*P* value
Sex			0.446
Male	79 (73.15 %)	76 (68.47%)	
Female	29 (26.85%)	35 (31.53%)	
Age			0.125
<65	83 (76.85%)	75 (67.57%)	
≥65	25 (23.15%)	36 (32.43%)	
IASLC			0.125
IIIB	10 (9.26%)	23 (20.72%)	
IV	98 (90.74%)	88 (79.28%)	
ECOG			0.161
0-1	106 (98.15%)	105 (94.59%)	
2	2 (1.85%)	6 (5.40%)	
Pathologic types			0.425
Adenocarcinoma	82 (75.93%)	79 (71.17%)	
Squamous cell carcinoma	26 (24.07%)	32 (28.83%)	

Abbreviations: DDP: cisplatin; ECOG, Eastern Cooperative Oncology Group.

baseline characteristics between treatment groups. For categorical variables, both person count and percentage were shown. Kaplan-Meier method and log-rank test were used to obtain and compare the survival curves of PFS between different treatment groups. The difference of ORR between treatment groups were tested by Chi-Square tests. Unless specified, all statistical testing will be 2-tailed and performed at the 5% significance level. All the analyses were performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics and patients deposition

Between January 2014 and December 2017, 219 Chinese patients with advanced NSCLC, who met the selection criteria at our cancer center, were enrolled in this study. Patients were divided into the experimental group (DDP 75 mg/m^2, d1) and the control group (DDP 25mg/m^2, d1-3) subcohorts. Among, patients receiving cisplatin combining with pemetrexed, docetaxel, and paclitaxel were included in the outcomes analysis. Although the patients were not randomized to treatment, baseline patient characteristics were insignificantly different across several parameters in the treatment cohorts, which were true for age, gender, disease stage, and ECOG PS (Table 1). This study was composed of 155 (70.8%) male and 64 (29.2%) female, and the age was ranged from 18 to 70. Most patients were diagnosed at stage IV stage and were ECOG PS of 0-1.

Short-term efficacy

After completing 2 cycles of chemotherapy, each patient underwent imaging examination to evaluate the efficacy, such as chest and abdominal CT as well as brain MRI. In the experimental group, 66 patients achieved PR, 34 patients achieved SD, 8 patients achieved PD, and the ORR was 61.11%. In the control group, 18 patients achieved PR, 77 patients achieved SD, 16 patients achieved PD, and the ORR was 16.22%. The ORR response in the experimental group were significantly higher than that in the control group ($P < 0.0001$). The results are shown in Table 2.

Table 2
ORR in overall study cohort.

	Single high-dose DDP (n = 108)	Fractionated dose DDP (n = 111)	*P* value
CR (%)	0	0	<0.0001*
PR (%)	66 (61.11%)	18 (16.22%)	
SD (%)	34 (31.48%)	77 (69.37%)	
PD (%)	8 (7.41%)	16 (14.41%)	
ORR (CR+PR) (%)	66 (61.11%)	18 (16.22%)	<0.0001*

Abbreviations: CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
* Significant difference in statistics.

Table 3
Adverse events in 2 groups.

	Single high-dose DDP (n = 108) No. (%)		Fractionated dose DDP (n = 111) No. (%)	
	I-II AE	III-IV AE	I-II AE	III-IV AE
Nausea	91 (84.26%)	17 (15.74%)	90 (81.08%)	21 (18.92%)
Vomiting	56 (51.85%)	12 (11.11%)	73 (65.77%)	29 (26.13%)
Reduced appetite	88 (81.48%)	20 (18.52%)	76 (68.47%)	35 (31.53%)
Hiccups	17 (15.74%)	2 (1.85%)	12 (10.81%)	3 (2.70%)
Increased serum creatinine	7 (6.48%)	0 (0.0%)	13 (11.71%)	0 (0.0%)
Leukopenia	77 (71.30%)	8 (7.41%)	83 (74.77%)	13 (11.71%)
Thrombocytopenia	9 (8.33%)	0 (0.0%)	14 (12.61%)	0 (0.0%)
Anaemia	12 (11.11%)	0 (0.0%)	27 (24.32%)	0 (0.0%)

Toxicity

All patients were evaluable for toxicities (Table 3). The observed toxicities were mild and patients showed good compliance to treatment. Toxicity mainly includes digestive tract reaction, nephrotoxicity, and myelosuppression. The digestive tract reactions included nausea, vomiting, loss of appetite, and hiccups; nephrotoxicity included increased serum creatinine and bone marrow suppression mainly included leukopenia, thrombocytopenia, and anemia. The incidence of nausea in the experimental group was similar to that in the control group, but the incidence of III-IV vomiting in the experimental group was lower than that in the control group (11.11% vs 26.13%). The incidence of I-II hiccups in the experimental group was higher than that in the control group (15.74% vs 10.81%). None of the patients had III-IV degree nephrotoxicity. Myelosuppression mainly manifested as leukopenia. In the experimental group, the incidence of I-II degree of leukopenia was 71.30%, and the III-IV degree was 7.41%, which was 74.77% and 11.71% respectively in the control group. A small number of patients have a decrease in mild platelets and hemoglobin (see Table 3 for the results). All adverse reactions can be controlled after symptomatic treatment.

Progression free survival

The mean PFS of the experimental and control groups was 8.815 ± 0.497 months and 8.459 ± 0.766 months respectively, with no statistical significance ($P = 0.5214$) in Fig. 2.

For lung adenocarcinoma, the mean PFS of the experimental and control groups was 9.232 ± 0.550 months and 9.013 ± 0.953 months respectively, with no statistical significance ($P = 0.7743$) as shown in Fig. 3. For squamous cell carcinoma, the mean PFS of the 2 groups was 6.667 ± 0.745 months and 7.094 ± 1.223 months respectively, with no statistical significance ($P = 0.7722$) as shown in Fig. 4.

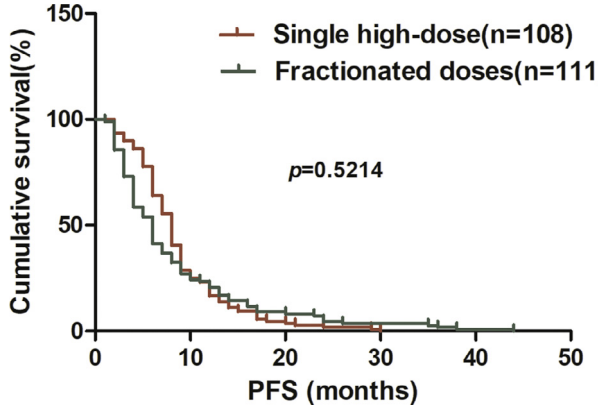

Fig. 2. Kaplan-Meier analysis of cumulative progression-free survival (PFS) of the experimental and control groups in both lung adenocarcinoma squamous cell carcinoma.

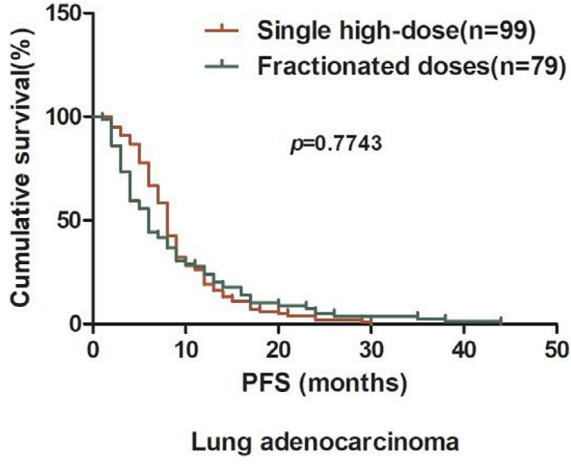

Fig. 3. Kaplan-Meier analysis of progression-free survival (PFS) of the experimental and control groups in lung adenocarcinoma.

Discussion

Cisplatin is one of the most effective chemotherapeutic drugs for patients with advanced NSCLC.[14] DDP combined with pemetrexed,[15,16] docetaxel,[17] paclitaxel,[18] gemcitabine,[19] and other drugs have been widely used clinically in advanced NSCLC. DDP is a high-efficiency, broad-spectrum antitumor drug. It is a cell cycle nonspecific anticancer drug that can cross link into the DNA of tumor cells to destroy its function and inhibit cell mitosis.[20,21] Multiple strategies for improving the efficacy of chemotherapy have been explored by applying novel antitumor agents, different schedules, and new combination regimens. Given the theory that cells can be killed by higher doses of chemotherapy drugs but can be resistant to lower doses of the same drug, high-dose chemotherapy with some promising results became a popular yet controversial treatment. The antitumor effect of DDP is related to the concentration, if the local concentration is doubled, and the effect of killing tumor cells would increase several times.[22] The therapeutic effect is positively correlated with the concentration to some extent,[23] and combination chemotherapy is more effective.

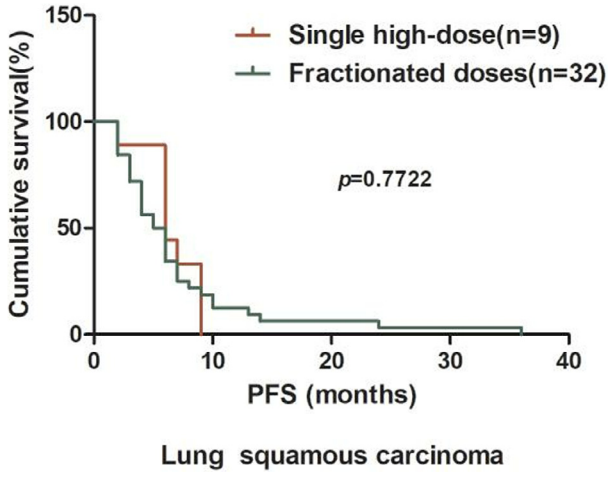

Fig. 4. Kaplan-Meier analysis of progression-free survival (PFS) of the experimental and control groups in squamous cell carcinoma.

Single high-dose cisplatin is a commonly used chemotherapy regimen in the world, however, the adverse reactions also cause physical and mental harm to patients more or less.[24-26] At present, fractionated doses DDP is used in most hospitals in China. Although many doctors have begun to try a single dose of cisplatin, there are still few studies on the comparison of efficacy and toxicity between the 2 regimens.

The present study showed that single high-dose DDP was significantly more effective than fractionated doses DDP, because the anti-tumor effect of DDP is related to the concentration as mentioned above. But there was no significant difference in PFS between the 2 groups. There was no difference in PFS between squamous cell carcinoma and adenocarcinoma as shown in Fig. 2. The main side effects of DDP were gastrointestinal reactions, impaired renal function, and myelosuppression. In this study, because of the application of oral aprepitant combined with intravenous antiemetics, the digestive tract reaction was less. It should be noted that high-dose DDP chemotherapy should be taken care of to prevent its toxic effects on the kidneys. After hydration, diuresis and close monitoring of 24h urine volume, we found that it can reduce the nephrotoxicity and minimize the toxicity of high dose DDP to the kidney.

Conclusion

Taken together, we believe that high-dose DDP should be a more effective treatment for advanced NSCLC. After adequate antiemetic,[27,28] hydration[29,30] and diuretic treatment, the side effects can be reduced to a minimum. Considering the effectiveness-toxicity, high-dose DDP treatment of NSCLC is in line with China's national conditions and is worthy of first-line treatment of advanced NSCLC, which is worthy of clinical promotion.

Our study may have several inherent limitations, such as its retrospective nature, a small sample size, and lack of OS. All these factors may cause biases and affect the power and significance of the finding. In future, prospective cohort studies are worthy to be conducted to gain a better insight into the methods of DDP application in Chinese patients with NSCLC and to strengthen our conclusion.

Conflict of interest

The authors have no conflicts of interest to disclose.

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