Research Paper

Clinical Efficacy of Cisplatin Intrapleural Perfusion with Pemetrexed Disodium for Lung Adenocarcinoma with Malignant Pleural Effusion and its Influence on Pleural Effusion Carcinoembryonic Antigen Levels

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This paper analysed the clinical efficacy of cisplatin intrapleural perfusion with pemetrexed disodium in the treatment of lung adenocarcinoma complicated with malignant pleural effusion and its influence on carcinoembryonic antigen levels in pleural effusion. 105 patients having lung adenocarcinoma with malignant pleural effusion who were admitted between July 2018 and July 2022 were selected and divided into research (n=55) and control group (n=50). Patients of the research group received cisplatin intrapleural perfusion with pemetrexed disodium and the control group patients were treated with carboplatin intrapleural perfusion along with pemetrexed disodium was given. Data of clinical efficacy, adverse reactions like fatigue, fever, gastrointestinal discomfort, decreased white blood cell count and reduced neutrophil count were analysed. Similarly pleural effusion volume, pleural effusion tumor markers like carcinoembryonic antigen, neuron specific enolase and pulmonary function were comparatively analysed. Further, maximal voluntary ventilation and forced expiratory volume in 1 s/forced vital capacity were collected for comparative analysis. Results showed higher total effective rate of treatment with markedly lower incidence of adverse reactions and smaller pleural effusion volume in research group compared with control group. Besides, evidently reduced levels of pleural effusion tumor markers and elevated pleural effusion indices in research group *vs.* control group were determined after treatment. It is suggested that cisplatin intrapleural infusion with pemetrexed disodium is effective in the treatment of lung adenocarcinoma with malignant pleural effusion, which can significantly inhibit carcinoembryonic antigen levels, reduce pleural effusion volume and improve pulmonary function while ensuring treatment safety.

Key words: Cisplatin, pemetrexed disodium, lung adenocarcinoma, pleural effusion, carcinoembryonic antigen

Malignant Pleural Effusion (MPE) is produced when metastatic cancer cells infiltrate thoracic lymph nodes and pleura, leading to fluid accumulation and reaction of tumors with immune cells, stroma and soluble factors, thus promoting malignant processes such as tumor proliferation and Epithelial-Mesenchymal Transition (EMT) [1,2]. MPE is common in patients with Lung Adenocarcinoma (LUAC), with a risk of up to 40 %, resulting in symptoms such as pain, chest tightness, shortness of breath, palpitation and inability to lie flat, which negatively affects the quality of life of patients resulting in adverse outcomes[3,4]. Common treatment strategies for patients with LUAC complicated with MPE include systemic chemotherapy, immunotherapy, molecular targeted therapy and intrathoracic infusion of chemotherapy drugs, but all with unsatisfactory curative effects, warranting treatment optimization[5-8]. Therefore, this study intends to explore new treatment options for LUAC+MPE patients, in the hope of contributing to the management optimization of this disease.

As an anti-tumor angiogenesis drug, pemetrexed disodium can be used to treat Non-Small Cell Lung Cancer (NSCLC) and Malignant Pleural Mesothelioma (MPM), and its inhibitory effect on tumor growth is related to the inhibition of cellular

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replication by disrupting intracellular folate-dependent metabolic processes[9,10]. Intravenous chemotherapy with pemetrexed disodium has also shown its effectiveness in controlling Pleural Effusions (PE) accumulation[11]. In addition, evidence has demonstrated the significant inhibitory action of intrapleural chemotherapy drugs against PE formation, which not only has favorable curative effects and safety, but also has conducive effect thereby helping to improve the patients' quality of life[12,13]. Therefore, clinically, intravenous chemotherapy and pleural perfusion chemotherapy are often combined to treat LUAC with MPE. Cisplatin (DDP) has a good effect on tumor cells and can significantly reduce the risk of pleurisy and PE leakage[14]. Carboplatin (CBP) is a chemotherapeutic drug with good pharmacokinetic advantages when administered intrapleurally and belongs to the platinum chemotherapy drug similarly like DDP, which has certain advantages in tolerability[15].

This study intends to compare and analyze the clinical effect of CBP or DDP intrapleural perfusion+pemetrexed disodium in the treatment of LUAC complicated with MPE, in an attempt to provide an optimized scheme for the treatment of such a patient population.

MATERIALS AND METHODS

General information:

In this study, 105 LUAC+MPE individuals admitted consecutively to our hospital between July 2018 and July 2022 were selected as the research participants strictly following the inclusion and exclusion criteria as described in this study. All the patients were divided into research group and control group, with 55 and 50 patients respectively. The patients of research group received DDP intrapleural perfusion+pemetrexed disodium while the patients of control group received CBP intrapleural perfusion+pemetrexed disodium. Research and control groups showed no notable difference in baseline data ($p>0.05$) and were clinically comparable. This study was approved by the Ethics Committee of DongYang People's hospital. Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Inclusion criteria:

Patients who were diagnosed as LUAC complicated with MPE by pathology; patients with chest Computerized Tomography (CT) and PE cytology; patients having intact medical records with an expected survival time of >3 mo and patients who did not undergo chemotherapy, targeted therapy or any other anti-tumor treatments in the recent month were included in the study.

Exclusion criteria:

Patients with serious cardiovascular, lung, brain and kidney dysfunction; patients who were allergic to the medication used in this study; patients who previously had the history of drug injection for PE; pregnant and lactating women and patients with MPE caused by non-lung cancer were excluded from the study.

Treatment method:

Patients in both the groups were given intravenous chemotherapy with pemetrexed disodium, as per the instructions manual of the drug. Dexamethasone tablets, folic acid tablets and vitamin B12 tablets were used for pre-treatment. During intravenous chemotherapy, close attention to the patient's body temperature, blood pressure, breathing, heart rate, pulse and other vital signs, and the occurrence of any adverse reactions in real time were monitored. Once there were any abnormalities, the chemotherapy was terminated and corresponding measures were adopted for symptomatic supportive treatment. Following accurate positioning of the PE in both the groups, a pleural drainage tube was placed for intermittent drainage, which was carried out after full drainage of the PE.

The control group was given 300 mg of CBP which was dissolved in 20 ml of normal saline and was injected into the chest cavity. Similarly, the research group received 50 mg/m^2 DDP for fractional intrapleural perfusion. The drainage tube was clamped immediately after the primary perfusion and was re-opened after 24 h for secondary DDP perfusion.

Endpoints:

Clinical efficacy: The clinical efficacy of drug is categorized into three levels namely, marked effectiveness, effectiveness and ineffectiveness. Marked effectiveness means that the patient's PE

completely disappeared, the clinical symptoms such as chest pain, shortness of breath, dyspnea and fatigue were completely resolved, and all physiological indices returned to normal after treatment. Similarly, effectiveness refers to obviously reduced PE, ameliorated clinical symptoms and gradual return of various physiological indices to normal after treatment. While, ineffectiveness corresponds to little reduction or increase of PE after treatment, with persistent or even worsened clinical symptoms and no obvious changes in various physiological indices.

Total effective rate=(marked effectiveness cases+effectiveness cases)/total cases×100 %

Adverse Reactions (ARs): We mainly observed and recorded the patients with adverse reactions such as fatigue, fever, gastrointestinal discomfort, decreased White Blood Cell (WBC) count, and reduced neutrophil count. Subsequently, we calculated the rate of incidence of Ars between both the groups.

PE volume: PE volume in all the patients of the two groups was measured before and after treatment using B-ultrasonography.

PE tumor markers: 6 ml of blood sample was collected from all the patients for measurement of tumor markers. Then tumor markers such as Carcinoembryonic Antigen (CEA) and Neuron Enolase (NSE) were detected using electrochemiluminescence (ECL) immunoassay. The ECL immunoanalyzer (Cobas 8000) and kits were all supplied by Roche diagnostics.

Pulmonary Function (PF): PF was evaluated by comparative analysis between both the groups. PF refers to the ratio of Forced Expiratory Volume in 1 s (FEV1) to Forced Vital Capacity (FVC) (FEV1/FVC). Similarly, Maximal Voluntary Ventilation (MVV) was also measured using a lung function tester.

Statistical analysis:

Mean±Standard Error of Mean (SEM) was used for analyzing the statistical analysis and measurement of the data. Inter- and intra-group comparisons were carried out using independent sample t-test and paired t-test, respectively. Count data was represented by the ratio (percentage), and the comparison between the two groups was studied using Chi-square (χ^2) test. The collected experimental data was analyzed using Statistical Package of Social Sciences (SPSS) version 24.0, where $p<0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Baseline data such as age, gender, scores of Eastern Cooperative Oncology Group (ECOG) which is used for determining the patient's level of functioning, pathological site, smoking history and alcohol abuse history of the research and control groups was compared. It was observed that no marked differences were found ($p>0.05$) (Table 1).

The clinical effectiveness between the two groups was compared and the total effective rate of the research group was found to be 89.09 % which was significantly >70.00 % of the control group ($p<0.05$) (Table 2).

ARs observed during the treatment process between both the groups was analyzed comparatively. The analysis of the incidence of fatigue, fever, gastrointestinal discomfort, decreased WBC and reduced neutrophil count revealed an obviously lower total incidence in research group compared with the control group (18.18 % *vs.* 36.00 %), with statistical significance ($p<0.05$) (Table 3).

TABLE 1: BASELINE INFORMATION OF PATIENTS

Factors	Research group (n=55)	Control group (n=50)	χ^2/t	p
Age (y)	61.00±6.64	59.56±6.79	1.098	0.275
Gender (male/female)	29/26	28/22	0.113	0.737
ECOG (points)	2.55±0.63	2.36±0.66	1.509	0.134
Pathological site (left lung/right lung)	20/35	23/27	1.006	0.316
History of smoking (yes/no)	15/40	20/30	1.909	0.167
History of alcohol abuse (with/without)	18/37	14/36	0.276	0.599

TABLE 2: CLINICAL EFFECTIVENESS OF PATIENTS IN TWO GROUPS

Factors	Research group (n=55)	Control group (n=50)	χ^2/t	p
Marked effectiveness	29 (52.73)	22 (44.00)		
Effectiveness	20 (36.36)	13 (26.00)		
Ineffectiveness	6 (10.91)	15 (30.00)		
Total effectiveness	49 (89.09)	35 (70.00)	5.966	0.015

TABLE 3: ADVERSE REACTIONS OF PATIENTS IN TWO GROUPS

Factors	Research group (n=55)	Control group (n=50)	χ^2/t	p
Fatigue	2 (3.64)	3 (6.00)		
Fever	3 (5.45)	5 (10.00)		
Gastrointestinal discomfort	2 (3.64)	5 (10.00)		
Decreased WBC count	1 (1.82)	2 (4.00)		
Reduced neutrophil count	2 (3.64)	3 (6.00)		
Total	10 (18.18)	18 (36.00)	4.252	0.039

Further, PE volume of the research and control group was compared. Two groups had a similar amount of PE before intervention ($p>0.05$); PE volume in both the groups decreased significantly after intervention ($p<0.05$), with an even lower volume in the research group ($p<0.05$) (fig. 1).

Tumor marker levels in PE patients were compared between the research and control groups. The levels of tumor markers such as CEA and NSE in PE patients of both the groups were detected. No statistical differences were identified in these tumor makers between research and control groups before intervention ($p>0.05$). However, the indices of both the groups decreased to varying degrees after intervention ($p<0.05$), with lower CEA and NSE levels in research group *vs.* control group ($p<0.05$) (fig. 2).

PF indices before and after intervention of the two groups were detected. MVV and FEV1/FVC showed no significant differences between groups before intervention ($p>0.05$); the indices of both the groups increased significantly after intervention ($p<0.05$), with high post-interventional MVV and FEV1/FVC in research group *vs.* control group ($p<0.05$) (fig. 3).

MPE, which is a common complication caused by systemic diseases such as tumor, infection, or inflammation, mostly originates from pleural metastasis of lung or breast tumors, with LUAC being the most common medical complication[16,17]; presence of MPE usually indicates late or advanced stage of the disease. LUAC patients with MPE tend to have shorter overall survival and a higher risk of Epidermal Growth Factor Receptor (EGFR) mutations, which further increases the risk of its recurrence[18,19]. An effective treatment strategy is therefore urgently needed to prevent the progression of LUAC+MPE, which is of great significance to improve the clinical outcomes of such patients.

At present, there is still limited analysis comparing the clinical application of pemetrexed disodium+CBP or DDP for LUAC+MPE. This study carries out relevant analysis in this condition and reports it in detail. In this study, the total effective rate was statistically higher in research group than in the control group (89.09 % *vs.* 70.00 %), indicating superior clinical effectiveness of DDP+pemetrexed disodium than CBP+pemetrexed disodium, similar to the results reported by Rodríguez-Abreu *et al.*[20].

CBP is known to be a cell cycle non-specific chemotherapy drug with a concentration-dependent therapeutic effect, which can directly kill tumor cells without liver activation and can help to promote the absorption of effusion[21,22]. Intrapleural administration of DDP controls Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2)-dependent endothelial cell proliferation associated with the pathophysiological process of MPE[23]. While pemetrexed disodium inhibits

purine and pyrimidine synthesis by negatively regulating dihydrofolate reductase, thymidylate synthase and other folate-dependent metabolic pathways, thus playing an anti-tumor therapeutic role[24,25]. The total incidence of ARs (e.g., fatigue, fever, gastrointestinal discomfort, decreased WBC and reduced neutrophil count) was found to be significantly lower in research group *vs.* control group (18.18 % *vs.* 36.00 %), suggesting that DDP intrapleural perfusion+pemetrexed disodium has good safety in the treatment of LUAC+MPE. In the study of Dong *et al.*[26], pemetrexed disodium+DDP intrapleural perfusion also showed good efficacy and clinical safety in the treatment of advanced non-squamous NSCLC patients complicated by MPE, which is similar to our research results. In addition, research group had significantly reduced PE volume after intervention, lower than the pre-interventional level and control group, demonstrating the outstanding effect of DDP intrapleural perfusion+pemetrexed disodium on reducing PE in LUAC+MPE patients. As reported by Chen *et al.*[27], DDP+pemetrexed disodium has definite efficacy in patients with MPM-mediated MPE, significantly reducing PE, alleviating symptoms, improving patients' quality of life and prolonging their survival. The PE CEA and NSE levels of research group reduced notably after intervention and were greatly lower compared with control group, suggesting that the treatment of DDP intrapleural perfusion+pemetrexed disodium has a significant down-regulation effect on the abnormal levels of tumor markers in PE in LUAC+MPE patients. Moreover, MVV and FEV1/FVC of research group were also significantly reduced after intervention, lower than those of control group, which indicates that DDP intrapleural infusion+pemetrexed disodium has a positive effect on improving PF in LUAC+MPE patients.

Conclusively, DDP intrapleural infusion+pemetrexed disodium can significantly enhance clinical efficacy in LUAC patients complicated with MPE with good drug tolerance, which can effectively reduce the PE volume, inhibit CEA and NSE levels in PE, and improve patients' PF, thereby providing new treatment directions and cognition for LUAC complicated with MPE.

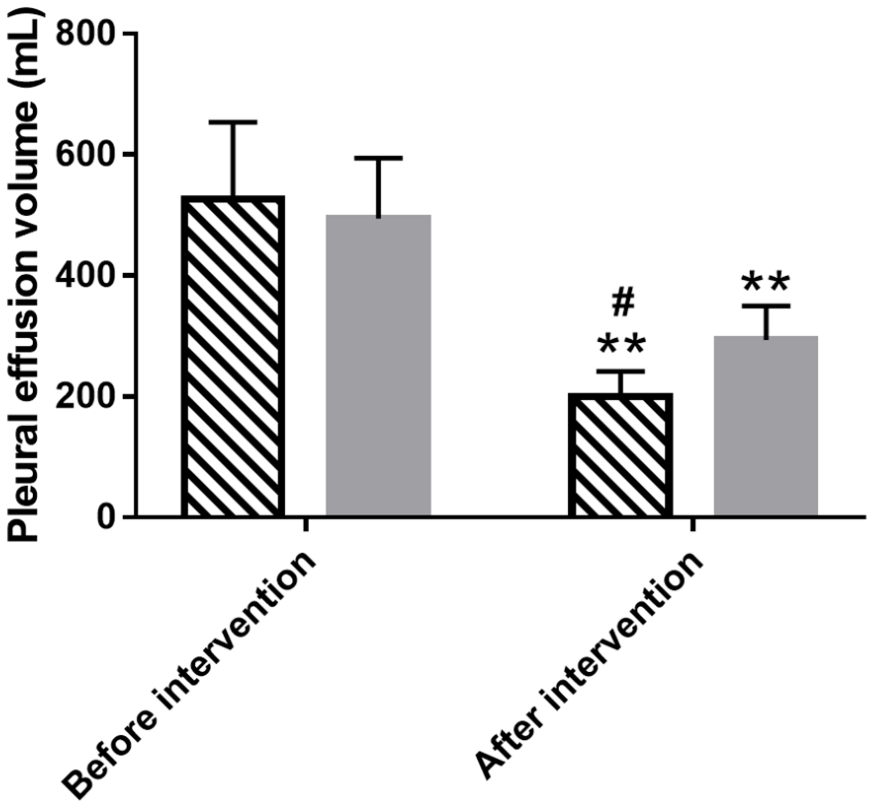

Fig. 1: Pleural effusion volume
Note: *p<0.05 *vs.* #p<0.05 compared with control group before treatment, (▨): Research group and (▬): Control group

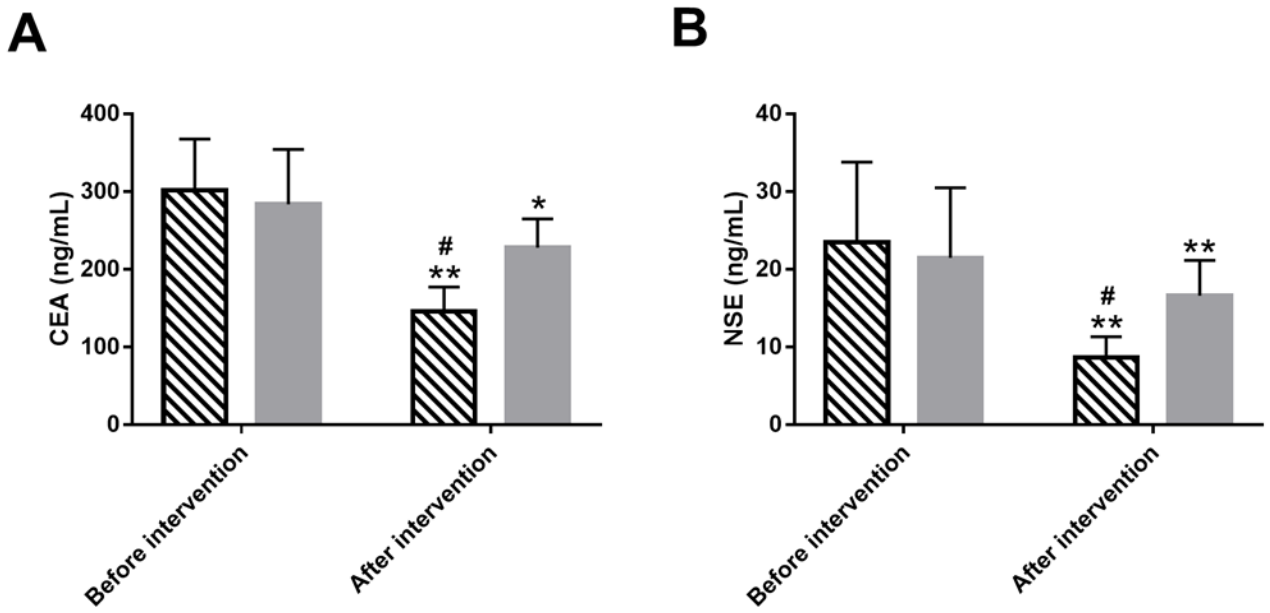

Fig. 2: Pre- and post-interventional tumor marker levels in PE in two groups, (A): CEA levels and (B): NSE levels
Note: *p<0.05 *vs.* #p<0.05 compared with control group before treatment, (▨): Research group and (▬): Control group

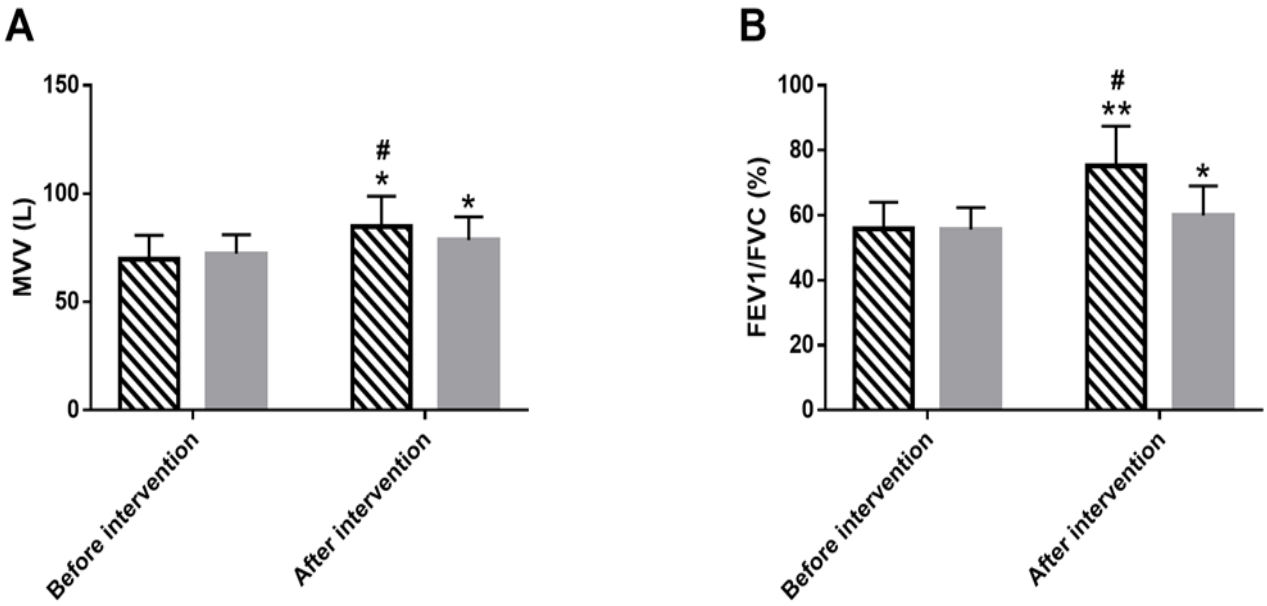

Fig. 3: Pre- and post-interventional PF between two groups, (A): MVV and (B): FEV1/FVC
Note: *p<0.05 *vs.* #p<0.05 compared with control group before treatment, (▨): Research group and (▬): Control group

Funding:

This study was supported by the 2021 public welfare Jinhua Science and Technology Research Plan Project (Project name: Exploration of a new mode of DOPS in the teaching of pleural and ascites cell morphology diagnosis and operation skills) with Project No: 2021-4-136.

Conflict of interests:

The authors declared no conflict of interests.

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This article was originally published in a special issue, "Drug Discovery and Repositioning Studies in Biopharmaceutical Sciences" Indian J Pharm Sci 2024:86(4) Spl Issue "1-7"