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Intrapleural combination therapy with lobaplatin and erythromycin for non-small cell lung cancer-mediated malignant pleural effusion

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Keywords
Erythromycin; intrapleural therapy; lobaplatin; malignant pleural effusion; non-small cell lung cancer.

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Abstract

Background: Malignant pleural effusion is a common complication of non-small cell lung cancer (NSCLC); however, treatment options remain limited. This study evaluated the safety and efficacy of sequential intrapleural therapy with lobaplatin and erythromycin for NSCLC-mediated malignant pleural effusion.

Methods: Fifty-six patients with NSCLC complicated with malignant pleural effusion were recruited for a prospective single-arm study from December 2014 to 2016; one patient dropped out. In addition to conventional systemic chemotherapy, lobaplatin and erythromycin were intrapleurally injected into subjects. Short and long-term responses were analyzed. The concentration of ultrafilterable platinum in the pleural effusion and plasma were detected at different time points. Incidences of severe adverse reactions were observed.

Results: In the 55 evaluable patients, the effective rate of pleural effusion was 81.8% after six weeks of treatment. Six and twelve months after treatment, the effective rates were 60% and 21.8%, respectively, and the one-year survival rate was 83.6%. The concentrations of lobaplatin in pleural effusion and plasma two hours after injecting 50 mg lobaplatin into the thoracic cavity were 13.763 ± 1.523 μg/mL and 1.120 ± 0.164 μg/mL, and 17 hours later were 1.961 ± 0.351 μg/mL and 0.578 ± 0.095 μg/mL, respectively. The rate of severe adverse reactions of the first cycle of systemic chemotherapy combined with lobaplatin and erythromycin did not significantly differ from the rate in the second cycle.

Conclusion: Intrapleural combination therapy with lobaplatin and erythromycin is a safe and efficient treatment for patients with NSCLC-mediated malignant pleural effusion.

Introduction

The incidence of pleural effusion in patients with lung cancer is 7–23%,[1] and 90–95% of cases involve malignant pleural effusion (MPE). MPE can lead to symptoms including dyspnea and chest pain. The median overall survival of patients with MPE is < 6 months.[2,3]

There is an urgent need for appropriate palliative care for patients with MPE.[4] British Thoracic Society (BTS) guidelines recommend using catheter drainage or pleurodesis to treat MPE. However, the local recurrence rate in the pleural cavity and the incidence of adverse reactions related to catheter drainage are very high.[5,6] Compared with intrathoracic injection, thoracoscopic pleural fixation with talcum powder is more complicated and costly, and a small number of patients may develop acute respiratory failure after administration.[6,7] Some patients develop pachynsis

pleural or multi-cavity pleural effusion after talc is deposited in the pleura.[8] Although pleurodesis by erythromycin has a strong adhesion effect, it is seldom used for MPE alone as it cannot prevent the proliferation of metastatic cancer cells.[9] Intrapleural therapy with platinum drugs, such as cisplatin, is widely used to treat MPE to kill the cancer cells, but these drugs are less effective for pleural adhesion.[10] Furthermore, cisplatin resistance is one of the problems of this treatment. As a third generation platinum analog, lobaplatin can overcome this shortcoming.[11–13] The combination of platinum and bevacizumab has a good curative effect for lung adenocarcinoma, but the effect on pleural adhesion is inadequate, slow, and expensive.[14] The curative effect of erythromycin combined with lobaplatin on MPE is unknown, as no studies have reported the pharmacokinetics, curative effect, or adverse reactions of injecting lobaplatin into the thoracic cavity. The objective of this study is to explore the efficacy and safety of the sequential intrapleural therapy with lobaplatin and erythromycin for MPE.

Methods

This prospective single-arm study was approved by the Academic Committee of Qilu Hospital of Shandong University (2014) 038 and registered with the China Clinical Trials Registry (registration number ChiCTR-OOC-14005452).

Patients

Fifty-six patients with non-small cell lung cancer (NSCLC) complicated with MPE were recruited for the study from December 2014 to 2016 at Qilu Hospital of Shandong University; one patient withdrew from the clinical research because of grade I chest pain caused by intrapleural lobaplatin therapy. Patient characteristics are listed in Table 1.

The inclusion criteria were: (i) age 25–75 years; (ii) histopathologically or cytologically confirmed NSCLC and MPE; (iii) chest computed tomography (CT) or ultrasound showed pleural effusion of a depth ≥ 3cm; (iv) physical status score (Eastern Coooperative Oncology Group [ECOG] performance status [PS]) 0–2 points; and (iv) presence of dyspnea. The exclusion criteria were: (i) expected survival duration < 2 months; (ii) hemoglobin < 110g/L, white blood cell count ≤ 3.0×10^9/L, neutrophils < 2.0×10^9/L, platelet < 150×10^9/L; (iii) severe cardiac insufficiency and a blood test result of transaminase and creatinine < 1.5 times the upper normal limit; (iv) a history of radiotherapy, or antiangiogenic, tyrosine kinase inhibitor, or intrapleural therapy; (v) multiloculated or bilateral pleural effusion; (vi) chylothorax or atelectasis; (vii) allergy to lobaplatin or erythromycin; (viii) pregnant or lactating women; and (ix) patients or caregivers that refused to sign consent.

Table 1 Baseline demographic and clinical characteristics

Catalogue	Total
Sample size	55
Age (years)	
Median	65
Range	35–75
Gender N (%)	
Male	29 (52.7)
Female	26 (47.3)
Performance status	
≤ 1	8 (14.6)
2	47 (85.5)
Pleural effusion depth (cm)	
≤ 5	8 (14.6)
> 5	47 (85.5)
First cycle chemotherapy, *n* (%)	
Carboplatin + pemetrexed	37 (67.3)
Carboplatin + docetaxel	15 (27.3)
Carboplatin + gemcitabine	3 (5.5)

Treatment protocol

Lobaplatin (50 mg) was dissolved in 5 ml sterile water, diluted with 100 ml physiological saline, and injected into the pleural cavity. The catheter was clamped after therapy. Pleural effusion (10–20 ml) was sampled at 2 and 17 hours after intrapleural injection to detect the lobaplatin concentration. Full drainage of pleural effusion was completed after 24 hours of treatment.

Chest X-ray and ultrasound were then performed to ensure that the maximum depth of pleural effusion was <3 cm and no pulmonary atelectasis or atelectasis was detected. Lidocaine (dosage of 3 mg/kg, maximum dose <250 mg[5]) was diluted with normal saline and injected into the pleural cavity. Morphine (8–10 mg) was subcutaneously injected approximately three minutes later for local anesthesia, and the diluted erythromycin (0.5 g) dissolved in 5% intravenous glucose solution (100 ml) was injected into the chest cavity. The catheter was clamped after therapy and the subjects were asked to turn over every 10 minutes to encourage full access of the delivered drugs to the chest wall.

The catheter was then clamped for two hours after pleurodesis. A one-time use of negative pressure drainage device, a wound suction set (1000 ml, Shanghai Cao Yang Medical Supplies, Shanghai, China) was then used to thoroughly drain the pleural effusion. When the drainage fluid reached < 150 ml/24 hours and a chest X-ray examination showed 90% lung recruitment, the drainage catheter was removed. If the drainage effusion continued at > 150 ml/24 hours for more than two days, intrapleural therapy of

erythromycin (0.5 g) was repeated. Erythromycin applications should not be repeated more than three times.

Pleural effusion and blood were taken at 2 and 17 hours after administering intrapleural lobaplatin therapy. High-performance liquid chromatography was used to determine the lobaplatin level in plasma and pleural effusion.

Four cycles of conventional systemic chemotherapy were performed, with the first cycle administered two or three days after injecting erythromycin into thoracic cavity. Regimens of carboplatin combined with pemetrexed or docetaxel were used for patients with pulmonary adenocarcinoma and carboplatin combined with docetaxel or gemcitabine for patients with squamous cell lung cancer. As an intrapleural injection of lobaplatin leads to partial absorption of the drug into the blood, the carboplatin dose was adjusted according to a target area under the curve (AUC) of 3, while the doses of pemetrexed, docetaxel, and gemcitabine remained the same.

The patients were followed-up via examination and chest CT six weeks, and six and 12 months after the erythromycin injection into the thoracic cavity. The effects of pleural effusion and the solid tumor were evaluated at six weeks. The effective rate of pleural effusion was evaluated at six and 12 months, as well as the one-year survival rate. The incidence of severe side effects in the first cycle of systemic chemotherapy (combined with intrapleural injection of lobaplatin and erythromycin) was observed and compared with the second cycle of systemic chemotherapy alone.

Evaluation of efficacy and safety

Responses to treatment were determined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[15] A complete response (CR) is achieved when the accumulated fluid disappears and is stable for at least four weeks; a partial response (PR) when > 50% of the accumulated fluid has disappeared, symptoms have improved, and the remaining fluid has not increased for at least four weeks; stable disease (SD) when < 50% of the accumulated fluid has disappeared; and disease progression (PD) when the accumulated fluid has increased. The total efficiency is calculated by the sum of CR + PR.

According to RECIST, the effective rate is calculated as CR plus PR divided by the total number of cases (excluding dropout cases).[16] The United States National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAE-4) divides adverse events, such as bone marrow suppression, nausea, and vomiting, into five grades.[17] World Health Organization verbal rating scales (VRS), divide chest pain, caused by intrapleural therapy of lobaplatin and erythromycin-induced pleural inflammation, into levels I–III.[18]

The data were analyzed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Numerical variables following normal distribution were expressed as mean ± standard deviation, while those not subject to normal distribution were described by the median. Categorical variable data was described by *n* (%). A *t*-test was used to compare two numerical variables and the $\chi 2$ test to compare two categorical variables. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

A total of 55 patients completed the study, including 41 cases of adenocarcinoma (wild-type *EGFR* mutations) and 14 squamous cell lung cancer. All 55 patients underwent four cycles of systemic chemotherapy according to the National Comprehensive Cancer Network (NCCN) Guidelines for Non-Small Cell Lung Cancer versions 1–4. All patients were intrapleurally injected with lobaplatin and erythromycin during the first cycle of systemic chemotherapy. The average hospital stay during intrathoracic therapy and first-cycle systemic chemotherapy was 9.5 ± 0.9 days. The lung did not expand (trapped lung) in 55 patients. After the first cycle of systemic chemotherapy had begun, none of the patients repeated intrapleural therapy.

At follow-up six weeks after the administration of drugs into the thoracic cavity, none of the patients had died, two achieved CR of pleural effusion, and 43 achieved PR, with an effective rate of pleural effusion of 81.8% (45/55). Regarding the efficacy evaluation of solid tumors, none of the patients achieved CR, with 21 patients reaching PR and an effective solid tumor rate of 38.2% (21/55).

At follow-up six months after the administration of drugs into the thoracic cavity, three patients had died (1 from lung cancer, 2 from chronic obstructive pulmonary disease), while 33 cases with pleural effusion experienced PR; no CR was achieved. The effective rate of pleural effusion was 60% (33/55). At the 12-month follow-up, six patients had died (4 from lung cancer, 1 from chronic obstructive pulmonary disease, 1 from diabetes). The therapy was effective in 12 cases (all PR), and the effective rate

Table 2 Free lobaplatin concentration in pleural effusion and plasma

Location	Two hours after the therapy	Seventeen hours after therapy
In plasma (μg/mL)	1.120 ± 0.164†	0.578 ± 0.095†‡
In pleural effusion (μg/mL)	13.763 ± 1.523	1.961 ± 0.351§

†Plasma concentration compared with pleural effusion concentration ($P < 0.01$). ‡Plasma concentration at 17 hours compared to 2 hours ($P < 0.05$). §Pleural effusion concentration at 17 hours compared to 2 hours ($P < 0.01$).

Table 3 Incidence of > grade 3 bone marrow suppression and nausea and vomiting

Chemotherapy cycle	Sample size (*n*)	Leukopenia (%)	Anemia (%)	Thrombocytopenia (%)	Nausea and vomiting (%)
First	55	7.3	0	7.3	9.1
Second	55	9.1†	1.8†	3.7†	7.3†

†Rate of severe adverse reactions after the first cycle of systemic chemotherapy compared with the second ($P > 0.05$).

of pleural effusion was 21.8% (12/55). The one-year survival rate was 83.6% (46/55).

The concentration of ultrafilterable platinum in pleural effusion in all patients was significantly higher than in plasma at both 2 and 17 hours after injecting 50 mg lobaplatin. The concentration of ultrafilterable platinum 17 hours after injecting 50 mg lobaplatin was significantly lower than at two hours after injection both in plasma and pleural effusion (Table 2).

The adverse reactions observed included chest pain in 35.7% (20/56) patients within three weeks after intrapleural therapy: 21.4% (12/56) experienced grade I, 14.3% (8/56) grade II, and 0% (0/56) grade III (Table 3). Three cases of grade I chest pain were self-mitigated within 12 hours, including one patient who withdrew from the study. The 17 cases of chest pain were relieved within 24 hours. Two cases of low fever recovered within 24 hours and did not require treatment with antibiotics or antipyretic drugs. No incidences of empyema occurred. There were no significant differences in the incidence of adverse reactions (e.g. thrombocytopenia, anemia, thrombocytopenia, nausea, and vomiting) in the first cycle of systemic chemotherapy combined with intrapleural therapy compared to incidence in the second cycle of systemic chemotherapy.

Discussion

Both the BTS and NCCN recommend catheter drainage and pleurodesis as therapy for lung cancer mediated-MPE; however, few studies have been conducted to assess the efficacy of intrapleural combination therapy of erythromycin and platinum-based chemotherapy.[5] Talc pleurodesis (TP) is considered the most effective method of controlling MPE, with an effective rate reported at 60–90%.[5] Schafers and Dresler reported a TP success rate of 97% in 30 days, 95% in 90 days, and a non-recurrence rate of pleural effusion of 92% one year after TP until patient death.[19] Dresler *et al*. reported efficiency rates of thoracic spray TP pleurodesis and injection of TP pleurodesis of 82% and 67%, respectively; however, the incidence of respiratory complications was 14%, and the respiratory failure rate was 4%.[20] Animal experiments have shown that TP is deposited to the contralateral thoracic cavity within an hour after injection and is widely distributed in the bilateral lungs, and mediastinal and parietal pleura, which then leads to inflammatory changes in the bilateral lungs.[21] In addition, TP can lead to other serious complications, such as acute respiratory distress syndrome.[6] TP is not recommended for patients with MPE pulmonary collapse.[6] Davies *et al*. reported that there was no significant difference between catheter drainage and TP to reduce dyspnea for MPE patients.[22] The recurrence duration of pleural effusion after pleural drainage was short (mean 4.2 days), and the recurrence rate was high (97% in 1 month).[23]

Erythromycin can be used as an ideal pleural adhesion sclerosis.[7,24] Although the BTS does not recommend erythromycin as a pleural sclerosant,[5] some animal studies have detected pleural fibrosis after intrapleural injection of erythromycin,[9,24] and the pleural inflammation, which can lead to chest pain, is mild.[9] Balassoulis *et al*. reported that after catheter drainage and erythromycin, pleurodesis reached an effective rate of 88.2% for MPE in 34 patients. However, neither TP nor erythromycin pleurodesis can control the growth of local tumor cells in the pleural cavity.

Although the BTS and NCCN do not recommend it, clinicians widely use intrapleural chemotherapy with cisplatin and other anti-tumor drugs to treat MPE.[10,25] There is no cross-resistance between lobaplatin, cisplatin, and carboplatin. Lobaplatin is superior to cisplatin for the treatment of lung cancer.[11] However, medical evidence of the intrapleural use of lobaplatin is limited.

Dresler *et al*. reported an effective rate of short-term pleural effusion treated by TP of 82%.[20] Du *et al*. reported that after injecting bevacizumab and cisplatinum into the thoracic cavity, the effective rate of short-term pleural effusion was 83.33%, progression-free survival was 5.3 months, and OS was 10.3 months.[14] However, bevacizumab is expensive and cannot be used for squamous cell carcinoma. Our study shows that injecting lobaplatin and erythromycin into the thoracic cavity has a significant curative effect for MPE; at six weeks the efficiency of pleural effusion reaches 81.8%, and 60% and 21.8% efficacy at six and 12 months, respectively, consistent with the curative effects reported in the literature of TP pleurodesis and chest cavity injection of beacizumab.[14,20] Studies have reported that the median OS of patients with MPE is < 6 months;[2,3] however, in our study sample 83.6% of patients were alive a year later, indicating that the long-term efficacy of this therapy is reliable. The mechanism for this high efficiency may be a result of the combination of the cytotoxic function of lobaplatin for cancer cells and the high pleural

adhesion of the erythromycin. Cancer cell metastases to the pleura can lead to an increase in pleural fibrinolytic activity, which can result in pleurodesis failure.[5,26] Intrapleural chemotherapy with high lobaplatin concentration in the cavity can kill cancer cells and block the effect of fibrinolytic activity in the process. The results of our study show significantly greater ultrafilterable platinum concentrations in pleural effusion than in plasma, which is effective for killing cancer cells; our data supports this hypothesis.

Ultrafilterable platinum concentrations become lower than total platinum concentrations over time as a result of protein binding. The t1/2 final of total platinum in plasma is 6.8 ± 4.3 days, while for ultrafilterable platinum the t1/2 final is much shorter at 131 ± 15 minutes (measured from 2–11 hours).[27] Approximately 75% of the lobaplatin dose is excreted in the urine within 24 hours after dosing.[12] Total platinum (protein-bound platinum + ultrafilterable platinum) can still be measured after five days, whereas ultrafilterable platinum and intact lobaplatin can only be measured for up to 11 hours after lobaplatin administration.[27] In this study, ultrafilterable lobaplatin in the plasma was measured 17 hours after injecting lobaplatin into the chest cavity, which suggests that the effect of the buffer action of the pleural effusion slows down the process of absorption into the blood stream, in turn reducing the peak plasma concentration of lobaplatin. The literature reports that three hours after an intravenous (bolus injection) lobaplatin (50 mg/m^2) injection, the ultrafilterable platinum levels in plasma are still approximately 1.5 times higher than those in erythrocytes (2.1 ± 0.4 μmol/L).[27] In this study, the concentration of ultrafilterable platinum in plasma was 1.120 + 0.164 μg/mL (2.819 + 0.413 μmol/L) two hours after injecting 50 mg lobaplatin into the chest cavity, lower than reported in the literature after three hours.[27] This shows that the lobaplatin concentration in plasma is low after a thoracic cavity injection, resulting in few adverse reactions, and does not influence the efficacy of systemic chemotherapy. The concentration of ultrafilterable platinum in pleural effusion (137.635 ± 63.232 μg/mL; 1.961 ± 1.453 μg/mL) is significantly higher than in plasma (1.120 ± 0.664 μg/mL; 0.578 ± 0.463 μg/mL) 2 and 17 hours after injecting 50 mg lobaplatin into the chest cavity, indicating that the high concentration of lobaplatin in the thoracic cavity kills cancer cells in the pleural cavity.

Our results also show a low incidence of severe toxicity (34.5%), lower than that (100%) reported by Balassoulis *et al.*[7] The incidence of severe chest pain (grade III) (0%) was lower than that reported in the literature (7%) and after treatment with doxycycline pleurodesis (60%).[5,28] One reason is that lidocaine induces an anesthetic effect; another is that pleural inflammation caused by erythromycin pleurodesis is relatively minor.[9] In this study, neither chest infection nor death occurred.

All intrapleural therapies are completed in the first cycle of systemic chemotherapy, after which the carboplatin dosage is decreased. There was no significant difference in the incidence of bone marrow suppression (≥ grade 3), or nausea and vomiting in our study during the first cycle of systemic chemotherapy compared to the second. The rate of severe adverse reactions after the first cycle of systemic chemotherapy (combined with lobaplatin and erythromycin) was not significantly different from that in the second cycle, which shows that lobaplatin and erythromycin injections into the chest do not increase the adverse reactions caused by systemic chemotherapy.

The limitations of this study include the relatively small sample size, insufficient testing of blood and pleural effusion, and the lack of a control group. Further studies with a larger sample size are needed to validate these results.

Intrapleural combination therapy with lobaplatin and erythromycin for NSCLC-mediated MPE has many advantages, such as high efficiency, quick effect, few adverse reactions, and low cost. With the low plasma concentration of free lobaplatin and less severe systemic adverse reactions, this therapy is a safe and effective option for NSCLC-mediated MPE.

Disclosure

No authors report any conflict of interest.

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