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ORIGINAL ARTICLE

Randomized controlled trial of endostar combined with cisplatin/pemetrexed chemotherapy for elderly patients with advanced malignant pleural effusion of lung adenocarcinoma

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Summary

Purpose: *To evaluate the clinical efficacy and safety of endostar combined with cisplatin/pemetrexed (CP) chemotherapy for elderly patients with advanced malignant pleural effusion (MPE) of lung adenocarcinoma.*

Methods: *A total of 128 lung adenocarcinoma patients with MPE were randomly divided into two groups. Patients in the treatment group were treated with pemetrexed 500 mg/m², i.v., d 1, cisplatin intracavitary administration with a total dose of 75 mg/m², d 2, 5 and 8, and endostar intracavitary administration 45 mg, d 1, 4 and 7. Patients in the control group were treated with chemotherapy alone (pemetrexed and cisplatin and mode of administration were the same as for the treatment group.*

Results: *The effective rates (ER) of the treatment group and control group were 81.82 and 64.52%, respectively (x^2=4.906, p=0.027). The MPE control rates (DCRs) were 93.94 and 79.03%, respectively (x^2=6.168, p=0.013). The control rate of the treatment group was higher compared with the control group (p<0.05), especially during the first period when it was 54.55% (p=0.019); in addition, the recurrence rate was lower (9.68 vs 30.61%, p=0.005). Dyspnea, mood and overall health improved significantly in the treatment group patients. No statistically significant differences in side effects between the groups were noticed.*

Conclusion: *Intracavity endostar combined with intracavitary and i.v. pemetrexed and cisplatin had a significant effect on advanced MPE of lung adenocarcinoma. In addition, the quality of life (QoL) was significantly improved and the side effects were tolerable.*

Key words: *chemotherapy, endostar, lung adenocarcinoma, pleural effusion*

Introduction

Malignant tumors with MPE are common and morbidity and mortality from these tumors has been increasing in recent years. About 20% of lung cancer patients develop MPE, with lung adenocarcinoma being the most common cause. The development of most cases of MPE is closely correlated with tumor angiogenesis [1,2]. Folkman [3] stated "The growth and metastasis of tumors are correlated with angiogenesis. Antiangiogenesis is an effective tactic in treating tumors". These studies have provided a theoretical basis for further investigations on the antitumor mechanism of antiangiogenic agents [4,5].

A large number of studies have shown that endostar can significantly inhibit malignant tumors' endothelial cell proliferation and tumor angiogenesis [6-10]. Endostatin is an endogenous inhibitor of angiogenesis. It is a naturally occurring, 20-kDA

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c-terminal fragment derived from type XVIII collagen. Wang et al. [11] combined endostar with vinorelbine-cisplatin to treat non-small cell lung cancer (NSCLC) patients, and in the treatment group the total effective rate and total yield was significantly better compared with the control group, and the time to progression (TTP) was clearly prolonged. In addition, the survival rate and QoL scores were significantly higher in the treatment group and did not increase the adverse reaction rate. Based on these results, recombinant human endostatin (endostar) was listed as a first-line drug to treat NSCLC patients in China's version of the National Comprehensive Cancer Network (NCCN) guidelines and it was approved by the State Food and Drug Administration (SFDA) [11,12].

In the clinic, endostar is extensively used combined with chemotherapy for the treatment of NSCLC, and the results are good [13]. However, the effects of endostar intrathoracic perfusion for treating pleural effusions are not clear. The purpose of this study was to evaluate the effects of endostar combined with chemotherapy in the treatment of malignant MPEs.

Methods

Patients

A total of 128 patients diagnosed with lung adenocarcinoma were enrolled in the study. The diagnosis of all patients was pathologically or cytologically confirmed. Inclusion criteria were Karnofsky performance status (KPS) score 1–2, estimated survival time more than 3 months, and with measurable primary and metastatic disease allowing for an objective judgement of any therapeutic effect. All patients had medium to large amounts of MPE by B-ultrasound and computed tomography (CT) scan and had not received intra-thoracic chemotherapy within the last month. Patients were confirmed to not have chemotherapy contraindications, liver, kidney and heart dysfunction, or abnormal blood routine tests.

The patients were randomly divided into two groups using a random number table: the experimental group with 66 patients who received endostar combined with CP, and the control group with 62 patients who received CP alone. The two groups of patients showed no significant differences in sex or age (Table 1), allowing for a reliable comparison. This study was conducted in accordance with the declaration of Helsinki and after approval from the Ethics Committee of Kunming University of Science and Technology. Written informed consent was obtained from all participants.

Table 1. Comparison of the clinical data between the two groups

Group	*n*	*Gender (male:female)*	*Age, years, range*
Treatment	66	49:17	36-75
Control	62	47:15	38-76
p value		>0.05	>0.05

Treatment

Patients in the treatment group were treated with pemetrexed (pemetrexed, Pem, Eli Lilly, Indianapolis, USA) 500 mg/m^2, i.v. d1, (pemetrexed: 21 d/cycle, 3 cycles in total), intracavitary cisplatin (cisplatin, DDP, Yunnan Bio Valley Pharmacy Incorporated Company, China) with a total dose of 75 mg/m^2, d 2, 5 and 8, and intracavitary endostar (Shandong Xiansheng Maidejin Biological Pharmaceutical Co., Ltd. Tianjin, Yantai, China) 45 mg, d 1, 4 and 7, in a 21-d cycle. Patients in the control group were treated with pemetrexed 500 mg/m^2, i.v., d1 and intracavitary cisplatin with a total dose of 75 mg/m^2, d 2, 5 and 8. Evaluation of any therapeutic effect, toxicity, and side effects was performed after 3 cycles. Dexamethasone, folic acid, and vitamin B12 were administered before pemetrexed administration.

A central venous catheter was inserted into the thoracic cavity under B-ultrasound guidance and was connected to a drainage bag that made it convenient to record the volume of pleural effusion. Intrathoracic chemotherapy was performed after the pleural effusion was drained off, then the catheter was sealed for 24 hrs. In order to distribute the drugs evenly throughout the pleural cavity, the patients were required to change position frequently. Drainage was performed again 24 hrs later, and the catheter was removed when the volume of pleural effusion was less than 50 ml.

Symptomatic treatment was administered, and routine blood tests, tests of liver and kidney function, and an electrocardiogram were performed during the study. B-ultrasound was performed before each treatment cycle; if pleural effusion was present, the treatment continued as described above, but if the pleural effusion was absorbed or localized, cisplatin was administered intravenously. A chest CT scan and B-ultrasound were performed to evaluate the therapeutic effect after 3 cycles.

Pleural effusion evaluation criteria

Pleural effusion evaluation criteria followed the World Health Organization (WHO) cancer solutions therapeutic effect evaluation standards [14].

1. Complete response (CR): pleural effusion disappeared for more than 4 weeks.
2. Partial response (PR): pleural effusion was reduced more than 50% for more than 4 weeks.
3. Stable disease (SD): pleural effusion was reduced less than 50% or increased less than 25%.
4. Progressive disease (PD): pleural effusion increased more than 25% along with other signs of progressive disease.

The effective rate was equal to CR + PR. The pleural effusion control rate equaled the proportion of patients who did not need thoracentesis again (the deepest pleural effusion was less than 3 cm as detected by B-ultrasound).

Assessing the therapeutic effect

Response Evaluation Criteria in Solid Tumors (RECIST) [15] were applied to assess the therapeutic effect, categorized as CR, PR, SD or PD. The ER was equal to CR + PR. The disease control rate (DCR) was equal to CR+PR+SD.

Quality of life

The European Organization for Research and Treatment of Cancer QoL questionnaire (EORTC qlq-c30 v.3.0) is an instrument to assess the QoL in cancer patients worldwide [16] and was used to assess the QoL before treatment and after 3 cycles of chemotherapy.

Toxicity and side effects

Toxicity and side effects [17] were assessed by the NCI CTC3.0 standard for anticancer drug toxicity, which is classified as grades 0 to IV.

Follow-up

A 6-month to 1 year follow-up was performed for all patients. A chest CT scan and B-ultrasound were performed every 3-4 months.

Statistics

SPSS23.0 software was used to perform the statistical analyses. Differences in clinical data between the control and treatment groups were evaluated using x^2 test. The results were compared and analyzed with the t-test between the two groups and a p value <0.05 was considered statistically significant.

Results

Pleural effusion

Endostar combined with CP had a significant effect on malignant pleural effusion. The ERs of the treatment group and control group were 81.82% (54/66) and 64.52% (40/62), respectively, with statistical significance (x^2=4.906, p=0.027). DCRs were 93.94 and 79.03% respectively, also with significant difference (x^2=6.168, p=0.013) (Table 2). Analysis of MPE control showed that the control rate in the treatment group was significantly higher than in the control group (p<0.05), especially during the first cycle (54.55%; p=0.019), showing the treatment group had an earlier and stronger effect in controlling the MPE (Table 3).

Lesion evaluation

All 128 patients with advanced lung adenocarcinoma completed three cycles of chemotherapy. In the treatment group 6 patients achieved CR, 21 had PR, 21 showed SD, and 18 cases PD, with an ER 40.9% (27/66). The control group had 4 cases of CR, 19 cases of PR, 20 cases of SD, 19 cases of PD, with an ER 37.1% (23/62). However, there was no significant difference in ER between the two groups (x^2=0.195, p=0.659).

QoL

The EORTC qlq-c30 (v3.0) includes 5 functional scale (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, nausea and vomiting, pain), a scale for overall health and 5 single common symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea). Patients in both groups were asked to answer the questionnaire before treatment and before 3 cycles of chemotherapy. The results demonstrated that in terms of functional scales the patient emotional score was significantly higher than before treatment (p<0.05). The overall health has improved after treatment, and in the symptom scale, dyspnea improved substantially, although pain and fatigue decreased, but without statistically significant difference (p>0.05) (Table 4).

Table 2. Comparison of the therapeutic effect on malignant pleural effusion between the two groups

Group	*n*	*CR* *n*	*PR* *n*	*SD* *n*	*PD* *n*	*RR* *n (%)*	*DCR* *n (%)*
Treatment	66	19	35	8	4	54 (81.82)	62 (93.94)
Control	62	11	29	9	13	40 (64.52)	49 (79.03)
p value						0.027	0.013

RR: response rate (CR+PR) , DCR: disease control rate (CR+PR+SD)

Table 3. The pleural effusion control after each cycle

Group	*First cycle* *n (%)*	*Second cycle* *n (%)*	*Third cycle* *n (%)*
Treatment	36 (54.55)	49 (74.24)	52 (78.79)
Control	21 (33.87)	21 (33.87)	38 (61.29)
p value	0.019	0.022	0.030

Long-term effects

All patients were followed up for 6 months to 1 year. The 1-year survival rate of the treatment group was 78.79% (52/66) and for the control group it was 74.19% (46/62), with no statistical difference (x^2=0.376, p=0.540). After treatment, the recurrence rate of MPE in the treatment group was significantly lower than in the control group (x^2=7.82, p=0.005) (Table 5).

Adverse reactions

There were no complications such as hemopneumothorax or pneumothorax from the central venous catheter. The adverse reactions of the two groups were mainly myelosuppression, digestive tract reactions and fatigue caused by the chemotherapeutic drugs. Symptomatic therapy could alleviate most adverse reactions. The treatment group did not have any increase of adverse reactions relative to the control group and there were no occurrences of cardiac toxicity related to endostar (Table 6).

Discussion

Nearly 15% of patients with lung cancer develop pleural effusion, and almost 40% of patients newly diagnosed with NSCLC experience complications from pleural effusion [18]. Local treatment of lung cancer along with pleural effusion drainage is a first-choice option. A central venous catheter is used to drain the thoracic cavity thoroughly and infusing chemotherapeutic drugs into the cavity can increase the drug concentrations in the chest, causing pleural adhesions and also directly killing tumor cells. However, lung cancer with MPE is an advanced disease and usually has metastases to other organs and requires comprehensive therapy.

Research has shown that when tumor invasion or metastasis to the pleura causes vascular endothelial growth factor (VEGF) levels to rise, this increases vascular permeability and the formation of tumor neovascularization, which then leads to MPE development [19]. Verheul et al. [20] found that MPE had significantly elevated biological activity of VEGF, and therefore inhibiting the expression of VEGF may reduce the formation of MPE.

The above studies have shown that VEGF plays an important role in MPE formation, and inhibiting VEGF activity offers a theoretical basis in treating such effusions. Endostatin is an endogenous antiangiogenesis factor that can inhibit the activity of VEGF and also inhibit secretion of VEGF by tumor cells and reduce vascular perme-

Table 4. Comparison of the KPS scores after treatment between the two groups

Group	*n*	*+10 Score* *n*	*Constant* *n*	*-10 Score* *n*	*Resulting score* *n (%)*
Treatment	66	53	9	4	53 (80.30)
Control	62	37	15	10	37 (59.68)
p value					0.011

Table 5. Comparison of the pleural effusion relapse between the two groups

Group	*Relapse*	*Total*	*Recurrence rate (%)*	x^2	*p value*
Treatment	6	62	9.68	7.82	0.005
Control	15	49	30.61		

Table 6. Comparison of the toxic effects between the two groups

Toxic effects	*Treatment group (n=66)*				*Incidence (%)*	*Control group (n=62)*				*Incidence (%)*	x^2	*p value*
	I	*II*	*III*	*IV*		*I*	*II*	*III*	*IV*			
Leucopenia	16	12	3	0	46.9	15	11	2	0	45.2	0.042	>0.05
Anemia	12	6	0	0	27.3	14	4	0	0	29.0	0.049	>0.05
Thrombocytopenia	15	5	2	0	33.3	14	3	2	0	30.6	0.106	>0.05
Nausea, vomiting	17	12	2	1	48.5	16	11	2	0	46.8	0.038	>0.05
Tiredness, faintness	18	10	0	0	42.4	17	10	0	0	43.5	0.016	>0.05
Liver dysfunction	3	1	0	0	6.1	3	0	0	0	4.8	0.092	>0.05

ability, thus inhibiting the formation of hydrothorax [21]. In an animal model study, endostatin administered directly into the pleural space could control intracavitary tumor growth, effectively prevent MPE formation and recurrence, and provide synergistic effects with chemotherapeutic drugs [22].

Data from clinical studies of endostatin treatment of malignant pleural and peritoneal effusion support its efficacy. At an endostatin dose of 30-60 mg, once or twice a week, the total ER was 40-100%, and endostatin combined with chemotherapy was better than monotherapy, did not increase the adverse reactions to chemotherapy, and its cardiotoxicity was limited [23]. Liang et al. [24] reported that among 1523 patients with MPE, the treatment group received pleural perfusions of endostatin and cisplatin and the control group pleural perfusion of cisplatin only. The ERs were 76 and 48% in the treatment group and control group, respectively; the QoL improved by 69% in the treatment group *vs* 44% in the control group; and neither group experienced any heart toxicity. A comparison of the VEGF expression in the two groups before and after treatment showed that in the treatment group the expression of VEGF in patients' pleural effusion was significantly decreased after treatment.

Based on the above clinical results and background, this study evaluated endostar combined with CP or chemotherapy alone for the treatment of advanced lung adenocarcinoma with pleural effusion. The ER and the DCR of the treatment group were significantly higher than those in the control group (ER 81.82 *vs* 64.52%, DCR 93.94 *vs* 79.03%), and after each cycle the pleural effusion control rate in the treatment group was higher compared with the control group, especially early in the treatment, which means endostar combined with chemotherapy can effectively and quickly control the growth of pleural effusion, a result consistent with Liang et al. study [24].

Although there was no significant difference between the two groups in 1-year survival, the pleural effusion recurrence rate in the treatment group was much lower than in the control group (9.68 *vs* 30.61%). Even though widespread metastases resulted in death, most of the patients had no recurrence of pleural effusion and had a significantly improved QoL. The KPS score was significantly improved in the treatment group (80.3%) as compared with the control group (59.68%) (x^2=6.515, p=0.01.

The treatment group had a higher QoL and good tolerance to therapy. However, objective evaluation of the lesions showed no significant difference between the two groups (p >0.05). This may be because local application of endostar resulted in a relatively low blood drug concentration.

There were no significant differences in adverse reactions between the groups. Leukopenia, gastrointestinal tract reactions, and bone marrow suppression were common, most of them grade I-II, and all of them could be corrected after symptomatic treatment.

The major limitation of this study is that the number of patients was small and future studies on this topic should accrue higher patient numbers. Induction treatment with chemotherapy and endostar plus consolidation chemotherapy may also be reasonable treatment options.

In conclusion, endostar combined with CP chemotherapy for advanced lung adenocarcinoma with MPE has a therapeutic effect that is superior to conventional chemotherapy, and it effectively improved the patients' clinical symptoms such as breathlessness and difficulty breathing, and improved their QoL. It did not increase toxicity or adverse reactions to chemotherapy, and thus it seems useful for further clinical application.

Conflict of interests

The authors declare no conflict of interests.

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