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ORIGINAL ARTICLE

# Comparison of intra-pleural injection efficacy between Endostar and Bevacizumab combined with pemetrexed/cisplatin for the treatment of malignant pleural effusion in patients with epidermal growth factor receptor-/anaplastic lymphoma kinase-lung adenocarcinoma*

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## Abstract

**Objective** To compare intra-pleural injection efficacy and safety between Endostar and bevacizumab combined with pemetrexed/cisplatin for the treatment of malignant pleural effusion in patients with epidermal growth factor receptor (EGFR)-/anaplastic lymphoma kinase (ALK)-lung adenocarcinoma.

**Methods** Sixty-four pCVatients with EGFR-/ALK- lung adenocarcinoma with malignant pleural effusion (MPE) were admitted to the authors' hospital between January 2016 and June 2017. Patients were randomly divided into two groups: Endostar combined with pemetrexed/cisplatin (Endostar group); and bevacizumab plus pemetrexed/cisplatin (Bevacizumab group). They underwent thoracic puncture and catheterization, and MPE was drained as much as possible. Both groups were treated with pemetrexed 500 mg/m$^2$, intravenous drip (d1), cisplatin 37.5 mg/m$^2$ per time, intra-pleural injection (d1, d3). Patients in the Endostar group were treated with Endostar 30 mg per time, intra-pleural injection (d1, 3), and patients in the Bevacizumab group were treated with bevacizumab 5 mg/kg per time, intra-pleural injection (d1). Only one cycle of treatment was applied. MPE was extracted before treatment and on day 7 after treatment. The levels of vascular endothelial growth factor (VEGF) were determined using ELISA. Efficacy and side effects were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 criteria.

**Results** The objective response rates in the Endostar and Bevacizumab groups were 50.0% and 56.3%, respectively; there was no statistical difference between the groups ($P > 0.05$). After one cycle of treatment, the mean VEGF levels in MPE in both groups decreased significantly, and there was no significant difference in the degree of decline between the two groups ($P > 0.05$). In both groups, pre-treatment VEGF levels for patients achieving complete response were significantly higher than those for patients achieving stable disease + progressive disease ($P < 0.05$). No specific side effects were recorded.

**Conclusion** Endostar and Bevacizumab demonstrated similar efficacy in controlling MPE in patients with EGFR-/ALK- lung adenocarcinoma through an anti-angiogenesis pathway, with tolerable side effects. The levels of VEGF in MPE could predict the efficacy of intra-pleural injection of anti-angiogenesis drugs.

**Key words:** Endostar; bevacizumab; malignant pleural effusion; EGFR-/ALK-lung adenocarcinoma; cisplatin; pemetrexed; intra-pleural injection

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Malignant pleural effusion (MPE) is a common complication of lung cancer. Fifteen percent of newly diagnosed lung cancer patients experience MPE, which seriously affects quality of life, and suggests that the median survival time of patients is approximately 3.3 months, with a poor prognosis depending on the tumor subtype tumor and its clinical stage. For advanced non-small cell lung cancer (NSCLC), the incidence is as high as 50%, which can cause respiratory and circulatory failure, seriously affecting safety [1]. Presently, local therapeutic treatment approaches for MPE in patients with NSCLC mainly include thoracic puncture and drainage, and intra-pleural injection of drugs. Chemotherapeutic drugs are widely used, although with limited efficacy.

Vascular endothelial growth factor (VEGF) has been found to be a critical pathological factor in the occurrence and development of MPE. It can promote capillary permeability and angiogenesis. The levels of VEGF are significantly increased in MPE caused by lung cancer, mesothelioma, and breast cancer. Both endostatin and bevacizumab can inhibit VEGF. Clinical trials have shown that intra-pleural injection of either drug combined with cisplatin can effectively control MPE; however, the preferred agent remains unclear [2]. The purpose of this study was to compare intra-pleural injection efficacy and safety between Endostar and bevacizumab combined with pemetrexed/cisplatin in the treatment of MPE in patients with epidermal growth factor receptor (EGFR)-/anaplastic lymphoma kinase (ALK)- lung adenocarcinoma lung adenocarcinoma, and to preliminarily evaluate the utility of both drugs in the treatment of MPE.

## Materials and methods

### Baseline

Sixty-four patients with EGFR-/ALK- lung adenocarcinoma with MPE were admitted to the authors' hospital between January 2016 and June 2017. All patients were diagnosed with pathologically confirmed adenocarcinoma, and EGFR-/ALK- using gene detection methods. After providing informed consent, the patients were randomly divided into two groups: Endostar combined with pemetrexed/cisplatin group (Endostar group); and bevacizumab plus pemetrexed/cisplatin group (Bevacizumab group). General information for the two groups is summarized in Table 1.

**Table 1** Characteristic of patients

| Group | *n* | Male/Female | Age (years) | ECOG | | |
|---|---|---|---|---|---|---|
| | | | | 0 | 1 | 2 |
| Endostar | 32 | 18/14 | 58.2 (44–67) | 1 | 25 | 6 |
| Bevacizumab | 32 | 17/17 | 57.8 (43–68) | 0 | 27 | 5 |

### Inclusion and exclusion criteria

*Inclusion criteria*

All patients with EGFR-/ALK-lung adenocarcinoma were confirmed by histopathology; pleural effusion was moderate to large detected by computed tomography or ultrasound; malignant tumor cells were found in the effusion fluid; and routine blood, cardiac function, liver and kidney function, and electrolyte levels were normal.

*Exclusion criteria*

Patients with organ dysfunction, such as liver and kidney, those with a history of neurological or psychiatric disorders, and pregnant or lactating women, were excluded from this study.

### Protocol

All patients underwent thoracic puncture and catheterization monitored by ultrasound. MPE was drained as much as possible within 2 to 3 days. Both groups were treated with pemetrexed 500 mg/m$^2$, intravenous drip (d1), cisplatin 37.5 mg/m$^2$ per time, intra-pleural injection (d1, d3). Patients in the Endostar group were treated with Endostar 30 mg per time, intra-pleural injection (d1, 3), and patients in the Bevacizumab group were treated with bevacizumab 5 mg/kg per time, intra-pleural injection (d1). All patients were turned over every 20 min within a 2 h period after intra-pleural injection. Ultrasound was used to re-examine the MPE volume on day 21.

Three milliliters of MPE was extracted before treatment and on day 7 after treatment. The supernatant was centrifuged at 4000 rpm for 10 min at 4 °C. VEGF levels were determined using ELISA. The Human VEGF-A ELISA kit was purchased from R&D Systems (Minneapolis, MN, USA), and the microplate reader from Bio Rad Laboratories (Hercules, CA, USA).

### Endpoints

*Objective efficacy*

Objective efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria: Complete remission (CR), pleural effusion completely disappeared, lasting > 4 weeks; partial remission (PR), the amount of pleural effusion decreased > 30% compared with pre-treatment (based on the maximum depth of pleural effusion detected by ultrasound), lasting > 4 weeks; stable disease (SD), the amount of pleural effusion decreased by < 30% or increased by < 20% compared with pre-treatment; Progressive disease (PD), the amount of pleural effusion increased by > 20% compared with pre-treatment. The objective response rate (ORR) was calculated as: CR + PR. Side effects were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 criteria.

### Statistical analysis

SPSS version 16.0 (IBM Corporation, Chicago, IL, USA) was used to analyze the data. Numerical data are expressed as mean (± standard deviation), and the *t*-test was used for comparisons. Categorical data are expressed as percentage, and the $\chi^2$ test was used for comparisons; $P < 0.05$ was considered to be statistically significant.

## Results

### Comparison of clinical efficacy between the two groups

After the treatment period, 2 of 32 patients in the Endostar group achieved CR, 14 achieved PR, and the ORR was 50.0%. In the Bevacizumab group, 3 patients achieved CR, 15 achieved PR, and the ORR was 56.3%. There was no statistical difference between the two groups ($P > 0.05$) (Table 2).

### Relationship between VEGF levels in MPE and efficacy in the two groups

Before treatment, the mean VEGF level in MPE was 405.33 ± 127.78 pg/mL in the Endostar group and 402.87 ± 129.28 pg/mL in the Bevacizumab group; there was no statistically significant difference between the two groups (i.e., $P > 0.05$). After one cycle of treatment, the mean value of VEGF levels in MPE in both groups decreased significantly, with no significant difference in the degree of decline between the two groups ($P > 0.05$) (Table 3). Further analysis revealed that in both groups, pre-treatment VEGF levels in patients achieving CR were significantly higher than those in patients achieving SD + PD ($P < 0.05$) (Table 4).

### Side effects

In the Endostar group, changes in T wave and ST-T segment of electrocardiogram, and diarrhea or rash did not occur. In the Bevacizumab group, no mucosal hemorrhage or hemorrhage occurred at the orifice of the thoracic drainage catheter, and no proteinuria occurred. In the bevacizumab group, there were 3 patients with hypertension grade I and 3 patients with hypertension grade 2. Blood pressure was evenly controlled during treatment. There were no significant differences in digestive tract reactions, such as bone marrow suppression, liver and kidney dysfunction, or nausea and vomiting, between the two groups.

**Table 2** Comparison of clinical efficacy between two groups (*n*, %)

| Group | *n* | CR | PR | SD + PD | ORR |
|---|---|---|---|---|---|
| Endostar | 32 | 2 | 14 | 16 | 50.0% |
| Bevacizumab | 32 | 3 | 15 | 14 | 56.3%* |

* $P > 0.05$

**Table 3** The change in VEGF levels pre- and post-treatment (pg/mL, $\bar{x} \pm s$)

| Group | *n* | pre-treatment | post-treatment |
|---|---|---|---|
| Endostar | 32 | 405.33 ± 127.78 | 200.56 ± 64.10 |
| Bevacizumab | 32 | 402.87 ± 129.28 | 198.73 ± 63.85* |

* $P > 0.05$ compared with Endostar group

**Table 4** The relationship between pre-treatment VEGF levels in MPE and efficacy (pg/mL, $\bar{x} \pm s$)

| Group | *n* | CR | PR | SD + PD |
|---|---|---|---|---|
| Endostar | 32 | 452.19 ± 18.27 | 407.64 ± 72.07 | 300.23 ± 25.16* |
| Bevacizumab | 32 | 450.27 ± 16.68 | 409.43 ± 63.85 | 280.89 ± 12.86* |

* $P < 0.05$ compared with patients achieving CR

## Discussion

MPE, a type of malignant serous cavity effusion, refers to the abnormal increase of pleural fluid caused by malignant tumors involving the pleura or primary pleural tumors. MPE accounts for 25% of pleural effusion, 75% of which is caused by lung cancer, breast cancer, or lymphoma. Factors such as VEGF and matrix metalloproteinases (MMPs), which can induce vascular permeability, play a key role in the pathophysiological mechanism of MPE formation. Tumor cells can secrete autocrine VEGF and MMPs, both of which increase the permeability of the capillary network and, on the other hand, and promote neovascularization of tumors, and then increase the total infiltration area of the capillary intima [2]. In animal models, the levels of VEGF in MPE increased significantly. The increase in peritoneal microvascular permeability was observed in tumor-bearing mice, which were injected with exogenous VEGF, while ascites formation was inhibited when the mice were transfected with antisense oligonucleotides of VEGF [3]. It was also found that there was a significant increase of VEGF in MPE samples from patients with NSCLC who were at higher risk for distant metastasis [4]. Elevated messenger RNA expression levels of VEGF and endostatin in pleural effusion were more frequently detected in MPE than in pleural effusions caused by non-malignant diseases [5]. These studies provide new avenues for the treatment of malignant serous cavity effusion, especially MPE, in patients with NSCLC and high levels of VEGF.

Presently, the clinical treatment of MPE includes diuresis, restriction of sodium chloride intake, and systemic treatment, among others. Local treatment includes thoracic puncture and catheterization, intra-pleural administration of drugs, intra-pleural hyperthermic perfusion and surgical treatment. Many types of drug could be chosen for intra-pleural injection, with each having its own advantages and disadvantages.

Chemotherapeutic drugs often cause bone marrow suppression and digestive tract reactions; biological agents can cause fever; and pleural adhesion induced by talcum powder and other pleurodesis agents can cause pain and fever [2]. In contrast, with an improved understanding of the pathogenesis of MPE, anti-angiogenesis drugs targeting VEGF have attracted increasing attention due to their unique advantages of strong efficacy and fewer side effects. Of all these novel drugs, recombinant human endostatin (Endostar) and the monoclonal VEGF antibody bevacizumab have demonstrated promising therapeutic benefits for patients with NSCLC and MPE.

Endostar, a modification of endostatin, has many targets, including VEGF and fibroblast growth factor-beta, which can specifically act on vascular endothelial cells of newly formed blood vessels, inhibit endothelial cell migration, induce endothelial cell apoptosis and, thus, inhibit the growth of tumor vessels. Qin *et al* [6] performed a prospective, randomized controlled, national multi-center phase III clinic trial on intra-pleural injection of Endostar and/or cisplatin for the treatment of MPE and malignant ascites. The results showed that for MPE, the ORR of the combined group was 42%, which was significantly higher than that of the Endostar (32%) and cisplatin (22%) groups. The result is consistent with a series of small sample studies [7–10]. However, there remains a lack of consensus on what the dose, interval, and course should be for the administration of the drug. There has been no report on the evaluation of efficacy of intra-pleural administration of Endostar combined with cisplatin in systemic chemotherapy. Feng et al found that Endostar combined with cisplatin for the treatment of MPE in patients with NSCLC could reduce the levels of VEGF and HIF-1a in MPE [8], which was consistent with the findings of Zou *et al* [9].

Bevacizumab, a recombinant, humanized monoclonal anti-VEGFA antibody, was approved for use as first-line treatment for advanced non-squamous NSCLC by the United States Food and Drug Administration in 2006. Ma *et al* found that intra-pleural administration of bevacizumab alone was superior to cisplatin alone for the treatment of MPE and malignant ascites [11]. Han *et al* found that intra-pleural administration of bevacizumab combined with cisplatin was superior to cisplatin alone in the treatment of MPE when pemetrexed was intravenously administered. After one cycle of chemotherapy, the ORR in the bevacizumab group was 55.0%, which was higher than chemotherapy group (31.8%) [12]. Lower dose (5 mg/kg) of intra-pleural administration can also achieve better results, which was different from the 15 mg/kg dosage of intravenous chemotherapy [12–13]. Different studies have suggested that bevacizumab combined with cisplatin could effectively reduce the levels of VEGF in MPE [12–14]. Zhang *et al* found that inflammatory factors (interleukin [IL]-4 and IL-10) also decreased, suggesting that bevacizumab controls MPE through various pathways [14].

This was the first phase II study of intra-pleural injection of Endostar or bevacizumab combined with pemetrexed/cisplatin for the treatment of MPE in patients with EGFR-/ALK- lung adenocarcinoma. Only one cycle of therapy was applied. Pemetrexed/cisplatin is the standard first-line treatment for advanced EGFR-/ALK- lung adenocarcinoma, and anti-angiogenesis drugs can further improve its effect. Our results demonstrated no significant difference in the control of MPE between the two groups. The levels of VEGF in the pleural effusion fluid of both groups decreased significantly after treatment, but there was no significant difference in the degree of decline between the two groups. It was confirmed again that Endostar and bevacizumab had similar efficacy in controlling MPE through an anti-angiogenesis pathway. Previous studies have confirmed that the levels of VEGF in pleural effusion may be a predictor of efficacy for both drugs in controlling MPE [8–9, 12–14]. This study also confirmed that patients with higher levels of VEGF in pleural effusion before chemotherapy in both groups were more likely to benefit from anti-angiogenesis drugs to a similar extent. There was no difference in side effects between the two groups, and there were no specific side effects, suggesting that the use of anti-angiogenesis drugs in intra-pleural administration is safe and may be superior to intravenous methods.

There were several limitations to this study, the first of which was its small sample size. Patients underwent only one cycle of treatment, and whether both drugs have the same efficacy in controlling MPE under multi-course medication requires further study. Although currently used dosages of bevacizumab have been established, further adjustments may be necessary; however, the dose, interval, and course of Endostar remain unclear. Whether the two drugs can alleviate MPE to a greater extent after adjusting the regimen remains to be clarified. Some studies have suggested that hyperthermic perfusion chemotherapy may be a more advantageous method and, as such, adjusting the method of administration may be an option [15]. The patients were tested for the EGFR and ALK genes, but not for immunotherapy. Therefore, it is not clear whether they are more suitable for molecular-therapy targeting other genes and immunotherapy than for chemotherapy. Future studies investigating the efficacy of intra-pleural injection of anti-angiogenesis drugs when molecular-targeted therapy or immunotherapy is applied are warranted.

## Conflicts of interest

The authors declare no conflict of interest.

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