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Original Article

Clinical efficacy of pseudomonas aeruginosa injection combined with endostar in the treatment of malignant pleural effusion: a randomized trial

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Abstract: Objective: This study aims to investigate the therapeutic effects of combining pseudomonas aeruginosa injection (PAI) with endostar on patients with malignant pleural effusion and ascites. Methods: In this prospective study, a total of 105 patients with malignant pleural effusion and ascites admitted to our hospital from January 2019 to April 2022 were selected as research subjects. Among them, 35 patients treated with PAI combined with endostar were enrolled in the observation group, while 35 patients treated with PAI and another 35 patients treated with endostar were enrolled in the control groups. The clinical effectiveness and safety of all three groups were compared, and their relapse-free survival was examined over a period of 90 days. Results: After treatment, the remission rate and the relapse-free survival of the observation group were higher than those of the control groups ($P < 0.05$), but there was no difference between the control groups ($P > 0.05$). The main adverse effect observed was fever, which was more common in the PAI combined with endostar group than in the endostar-only group ($P < 0.05$). Conclusion: The clinical treatment of malignant pleural effusion and ascites can be improved by combining pseudomonas aeruginosa injection with endostar. This combination can increase the relapse-free survival of patients and improve the overall safety of treatment.

Keywords: Malignant pleural effusion and ascites, pseudomonas aeruginosa injection, endostar, recombinant humanized endostatin

Introduction

Malignant pleural effusion and ascites is one of the most challenging cancer-related disorders [1]. Current statistical data indicate that about 50% of patients with advanced malignant tumor will develop malignant pleural effusion and ascites [2]. The occurrence of malignant pleural effusion and ascites often indicates late-stage carcinoma with poor prognosis. If not managed properly, malignant pleural effusion and ascites can impede circulatory and respiratory functions, diminish quality of life, and even threaten patients' lives [3]. The principal method of clinical treatment involves actively removing the pleural effusion and ascites and preventing further decay of the disease. Thoracic perfusion of chemotherapy drugs is currently the main treatment method, but its clinical efficacy is limited, and the recurrence rate is high [4]. In recent years, thoracocentesis, pleurodesis, and perfusion have become common methods to treat pleural effusion and ascites in clinical practice. Among these, intrathoracic drainage combined with intrathoracic drug injection is the most effective and frequently used approach. Therefore, the cornerstone of effective pleural effusion and ascites treatment is judicious selection of injection drugs [5].

The pseudomonas aeruginosa injection (PAI) is derived from the inactive *P. aeruginosa* mannose sensitive hemagglutinin strain, diluted with phosphate buffer solution. PAI has been approved by the Chinese Food and Drug Administration as an adjuvant drug in the treatment of malignant tumors [6, 7]. Recent studies suggest that PAI can activate the immune system to inhibit tumor cell proliferation and pro-

vide effective anti-infection effects [8-10]. Endostar (EN), an independently developed recombinant humanized endostatin in China, inhibits VEGF expression and targets multiple anti-angiogenic roles without drug resistance [11]. Endostar can strongly suppress the proliferation, migration and tube formation of human endothelial cells, and exerts an anti-angiogenic function *via* VEGF-related signaling pathways. This demonstrates its significant contribution towards preventing malignant pleural effusion and ascites formation [12, 13].

The present treatment exhibits limited clinical effectiveness, and high recurrence rate. Consequently, it is imperative to uncover novel therapies that are more efficacious. In this prospective study, we scrutinize the safety and effectiveness of fusing PAI and endostar for the treatment of malignant pleural effusion and ascites, which has not been previously examined. The integration of PAI with endostar could offer an improved treatment paradigm with heightened effectiveness and enhanced safety.

Material and methods

Patient data

A total of 105 patients with malignant pleural effusion and ascites admitted to the department of digestive oncology of Civil Aviation General Hospital during the period of January 2019 to April 2022 were enrolled. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Civil Aviation General Hospital (No. 2020-25).

Inclusion criteria

The patients were confirmed by X-ray, ultrasound, and pleural effusion pathology examinations; the expected survival time was more than 8 weeks; and no chemotherapy, targeted therapy, or any other anti-tumor therapy had been administered in the month that preceded enrolment.

Exclusion criteria

Patients who have a projected survival time of one month or less, patients with multiple tumors, as well as those suffering from cardiovascular and cerebrovascular diseases, autoimmune deficiencies, organ impairments, or psychiatric ailments, and patients who are either pregnant or are currently in a lactation period, in addition to those who have been transferred to other medical facilities.

Patient grouping

The patients were sequentially numbered and randomly distributed into three groups: PAI group, EN group, and PAIE (PAI combined with EN, PAIE) group, each containing 35 cases, allocated through computer generated random number. Both the PAI group and EN group served as control groups, while the PAIE group was deemed the observation group. Age, gender, BMI, and pathological stage were not significantly different among the three groups ($P > 0.05$). Patients and their families were extensively briefed on the study details, and all participants provided written informed consent prior to the start of the study.

Treatment methods

Under the guidance of B-ultrasound, the drainage of pleural effusion and ascites was maximized within 48 hours followed by thoracic perfusion. The PAI group received PAI intraperitoneal (5 mL) or thoracic perfusion (10 mL). The EN group received endostar intraperitoneal (45 mg) or thoracic perfusion (60 mg). The PAIE group received a combination of PAI and endostar intracavitary perfusion with the following dosage: 5 mL PAI + 45 mg endostar intraperitoneally or 10 mL PAI + 60 mg endostar thoracic perfusion. Prior to the perfusion, each participant was given liver protection, antiemetic, stomach protection and other precautionary measures. Following the intracavitary perfusion, the participants were instructed to rest and adjust their position every fifteen minutes to ensure maximal drug distribution in the chest and abdominal cavity. Both before and after the perfusion, 5 mg of dexamethasone and 5 mL of lidocaine were administered to alleviate possible adverse reactions from the procedure. Each treatment course lasted for a duration of two weeks and the therapeutic effects were evaluated after two courses.

Research indicators and efficacy evaluation

As per the pleural effusion efficacy evaluation standards laid down by the World Health Organization, the quantity of pleural effusion

was ascertained with the help of B-ultrasound or computed tomography scan. Complete remission (CR): the patient had no clinical symptoms, the effusion completely disappeared and remained so for more than 4 weeks; Partial remission (PR): clinical symptoms improved, effusion reduced by over half, and pleural effusion drainage was not required for over 4 weeks; Stable disease (SD): no significant improvement of symptoms, effusion decreased by less than half, or increased by less than a quarter, or had no alteration; Progressive disease (PD): the amount of effusion increased significantly, the fluid needed to be pumped again within 4 weeks. All adverse events were documented and graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [3].

Follow-up of prognosis

Three cohorts of patients underwent a hospital-based follow-up over a period of three months. During this time, their remission period was scrutinized and the rate of their remission was documented. Furthermore, relapse-free survival (RFS) was characterized as the duration from the date of initial response (complete response [CR] or partial response [PR]) to their relapse date.

Statistical analysis

The SPSS 23.0 statistical software (IBM Corp., Armonk, NY, USA) was utilized to analyze and process the data, and Graph Pad 7 software was used to plot all the pictures. The measurement data were expressed as mean ± standard deviation and subsequently evaluated using the *t*-test. The enumeration data were expressed in percentage (%), and the Kaplan-Meier method was used for the calculation of the remission rate, with the Log-rank test utilized for comparison. The statistically significant difference was identified when $P < 0.05$.

Results

Baseline patient data

The baseline data of these patients have been summarized in **Table 1**. The clinical data of the three groups were comparable. As shown in **Figure 1**, all the 105 patients completed the treatment. Two weeks were used for a treatment course, with a total of two courses.

The remission of the three groups after treatment

After treatment, the PAI and EN groups predominantly exhibited complete remission (22.8%, 31.4%), whereas the PAIE group exhibited complete remission (34.3%), followed by partial remission (34.3%). Further assessment revealed that the objective response rate and disease control rate of the PAIE group were 68.6% (24/35) and 82.9 (29/35), which were significantly higher than those of the PAI group [40.0% (14/35) and 57.1% (20/35); P=0.016 and P=0.039, respectively] but not the EN group [54.3% (19/35) and 65.7% (23/35); P=0.220 and P=0.179, respectively] (**Table 2**). Additionally, patients who attained CR/PR demonstrated a 66.1-day relapse-free survival (RFS) in the PAIE group, which was considerably higher than that of the PAI group (49.6 days; P=0.002) and the EN group (55.7 days; P=0.044) (**Figure 2**).

Adverse reactions of the three groups after treatment

After undergoing treatment, various adverse reactions were reported, including fever, stomach ache, chest pain, fatigue, neutropenia, feeling sick and vomit, allergy, and transaminase elevation. The PAI group mainly experienced fever, feeling sick and vomit, stomach ache, while the EN group mostly reported fatigue, felling sick and vomit. In contrast, the PAIE group complained of fever, fatigue, with a limited number of patients suffering from stomach ache, neutropenia, allergy, and transaminase elevation. Notably, fever was the most frequently occurring adverse effect, and was more prevalent in the PAIE group in comparison to the EN group (P=0.017) (**Table 3**).

Discussion

Malignant pleural effusion and ascites are commonly observed in patients with end-stage tumors when the pleural cavity is involved. Normally, approximately 500-1,000 mL of pleural fluid is secreted and absorbed daily in order to maintain a dynamic equilibrium. However, malignant diseases can disrupt this balance and lead to malignant pleural effusion and asci-

Table 1. General characteristics of the patients

Characteristic	Group			*P*-value		
	PAI (n=35)	EN (n=35)	PAIE (n=35)	PAI vs. EN	PAI vs. PAIE	EN vs. PAIE
Male sex (%)	16 (45.7)	18 (51.4)	23 (65.7)	0.632	0.092	0.225
Age (years)	69.1 ± 11.5	70.2 ± 11.9	67.2 ± 11.6	0.700	0.504	0.300
ECOG performance status, n (%)				0.770	0.790	0.748
0	1 (2.9)	2 (5.7)	2 (5.7)			
1	13 (37.1)	11 (31.4)	14 (40.0)			
2	21 (60.0)	22 (62.9)	19 (54.3)			
Primary tumor, n (%)						
Stomach cancer	11 (31.4)	8 (22.9)	13 (37.1)	0.584	0.445	0.192
Cholangiocarcinoma and liver cancer	5 (14.3)	5 (14.3)	3 (8.6)	1.000	0.452	0.452
Pancreatic cancer	2 (5.7)	2 (5.7)	4 (11.4)	1.000	0.393	0.393
Colorectal cancer	2 (5.7)	7 (20.0)	2 (5.7)	0.074	1.000	0.074
Esophageal cancer	0 (0.0)	3 (8.6)	1 (2.9)	0.077	0.314	0.303
Ovarian cancer	5 (14.3)	5 (14.3)	3 (8.6)	1.000	0.452	0.452
Lung cancer	7 (20.0)	3 (8.6)	9 (25.7)	0.172	0.569	0.057
Breast cancer	3 (8.6)	2 (5.7)	0 (0.0)	0.643	0.077	0.151
Metastatic site, n (%)						
Peritoneum	11 (31.4)	0 (0.0)	9 (25.7)	0.001	0.597	0.001
Liver	7 (20.0)	11 (31.4)	5 (14.3)	0.274	0.526	0.088
Liver and lung	5 (14.3)	12 (34.3)	6 (17.1)	0.051	0.743	0.101
Abdominal lymph nodes	2 (5.7)	11 (31.4)	1 (2.9)	0.006	0.555	0.002
Pleura and lung	5 (14.3)	1 (2.9)	5 (14.3)	0.088	1.000	0.088
Pleura	3 (8.6)	0 (0.0)	3 (8.6)	0.077	1.000	0.077
Others	2 (5.7)	0 (0.0)	6 (17.1)	0.151	0.133	0.01
Effusion, n (%)						
Pleural effusion	10 (28.6)	3 (8.6)	14 (40.0)	0.031	0.314	0.002
Ascites	25 (71.4)	32 (91.4)	21 (60.0)	0.031	0.314	0.002

Notes: Categorical data were presented as number (percentage) and quantitative data as median value (interquartile range). Abbreviations: ECOG, Eastern Cooperative Oncology Group; PAI, Pseudomonas aeruginosa injection; EN, recombinant human endostatin (Endostar); PAIE, Pseudomonas aeruginosa injection combined with Endostar.

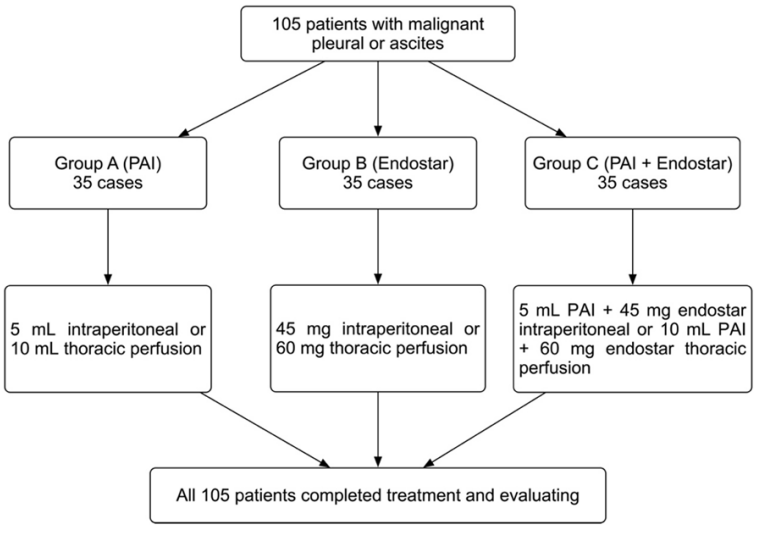

Figure 1. Participant flow through the study. Abbreviations: PAI, Pseudomonas aeruginosa injection.

tes. Excessive pleural fluid can have a profound impact on a patient's breathing, and may even result in apnea. Therefore, effective management of malignant pleural effusion and ascites is essential for improving the quality of life for patients with advanced disease.

Surgical pleurodesis is one method for managing malignant pleural effusion and ascites, but it is not commonly used in practice due to its traumatic nature [14]. Conservative treatment is usually preferred, which involves pleural effusion drainage as the

Table 2. Comparison of remission after treatment among the three groups

Treatment Response	Group			*P*-value		
	PAI (n=35)	EN (n=35)	PAIE (n=35)	PAI vs. EN	PAI vs. PAIE	EN vs. PAIE
Best overall response						
CR (%)	8 (22.8)	11 (31.4)	12 (34.3)			
PR (%)	6 (17.1)	8 (22.8)	12 (34.3)			
SD (%)	6 (17.1)	4 (11.4)	5 (14.3)			
PD (%)	15 (42.9)	12 (34.3)	6 (17.1)			
ORR (%)	14 (40.0)	19 (54.3)	24 (68.6)	0.231	0.016	0.220
DCR (%)	20 (57.1)	23 (65.7)	29 (82.9)	0.461	0.039	0.179

Notes: Objective response rate (ORR) = (CR + PR)/n; disease control rate (DCR) = (CR + PR + SD)/n, where CR is number of patients with complete remission, PR is number of patients with partial remission, SD is number of patients with stable disease, and n is total number of patients. Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; PAI, Pseudomonas aeruginosa injection; EN, recombinant human endostatin (Endostar); PAIE, Pseudomonas aeruginosa injection combined with Endostar.

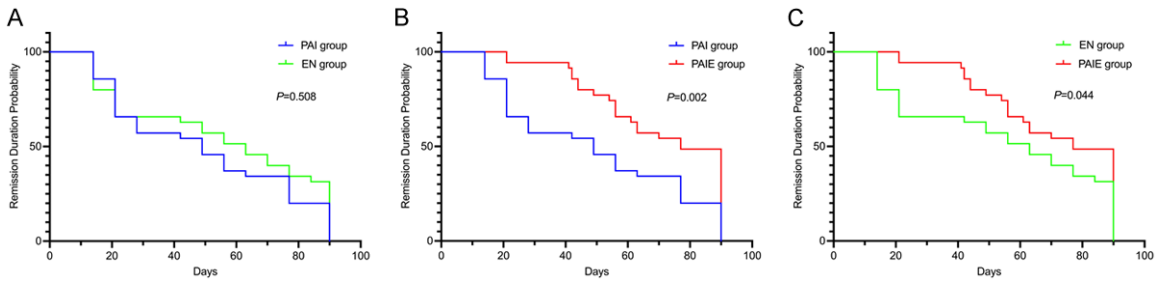

Figure 2. Kaplan-Meier estimate of remission duration. A. Patients treated with PAI or EN. B. Patients treated with PAI or PAIE. C. Patients treated with EN or PAIE. Abbreviations: PAI, Pseudomonas aeruginosa injection; EN, recombinant human endostatin (Endostar); PAIE, Pseudomonas aeruginosa injection combined with Endostar.

Table 3. Adverse events of patients

Adverse events	Group			*P*-value		
	PAI (n=35)	EN (n=35)	PAIE (n=35)	PAI vs. EN	PAI vs. PAIE	EN vs. PAIE
Fever	13 (37.1)	3 (8.6)	11 (31.4)	0.004	0.615	0.017
Stomachache	6 (17.1)	3 (8.6)	3 (8.6)	0.284	0.284	1.000
Chest pain	3 (8.6)	1 (2.9)	4 (11.4)	0.313	0.690	0.164
Fatigue	4 (11.4)	5 (14.3)	6 (17.1)	0.721	0.495	0.743
Neutropenia	1 (2.9)	2 (5.7)	2 (5.7)	0.555	0.555	1.000
Feeling sick and vomit	7 (20.0)	5 (14.3)	4 (11.4)	0.526	0.324	0.721
Allergy	2 (5.7)	0 (0.0)	1 (2.9)	0.151	0.555	0.314
Transaminase elevation	3 (8.6)	4 (11.4)	4 (11.4)	1.000	0.690	0.690

Note: Data are numbers of patients and data in parentheses are percentages. Abbreviations: PAI, Pseudomonas aeruginosa injection; EN, recombinant human endostatin (Endostar); PAIE, Pseudomonas aeruginosa injection combined with Endostar.

first step, followed by intrapleural perfusion with drugs as the second step. The drugs used for intrapleural perfusion include chemotherapeutic agents or immunosuppressants, or in combination [15, 16]. Intrapleural perfusion with chemotherapeutic agents promotes pleural adhesion, reduces pleural permeability, and decreases pleural effusion. Additionally, the cytotoxicity of chemotherapeutic agents also aids in controlling intrapleural metastasis [17].

Recent studies have indicated that utilizing PAI can effectively activate the Toll-like receptor of immune cells, which stimulates antigen presen-

tation in cell maturation, and consequently, this process triggers the differentiation and maturation of both natural killer and T cells, ultimately leading to the destruction of tumor cells [18]. Moreover, PAI has demonstrated significant efficacy in treating malignant pleural effusion and ascites, as well as hydropericardium [19]. Additionally, Genpeng *et al.* reported that intraoperative prophylactic use of PAI decreased the incidence of chylous leakage [20]. In 2005, China independently produced a recombinant human endostatin called Endostar. Endostar serves to inhibit angiogenesis by suppressing VEGF expression and proteolytic enzyme functionality. Currently, combining Endostar and chemotherapy is being used as a first-line treatment for several solid malignancies, including cervical cancer, ovarian cancer, and non-small cell lung cancer [21-23].

The incidence, progression, and metastasis of tumors depend on the growth of neovascularization. VEGF plays an impactful role in triggering angiogenesis [24]. Research indicates that the anomalous and disarrayed arrangement of tumor blood vessels affect the infiltration of lymphocytes, which leads to a decline in the normalization of tumor blood vessels due to reduced T cell infiltration [25]. T cells act as a key player in reinstating healthy tumor blood vessels by releasing interferon, with CD4+ T cells significantly decreasing the VEGF expression, promoting normalization of tumor blood vessels, thus further strengthening the infiltration of T lymphocytes. PAI works as an immunological adjuvant that elevates the immunological recognition abilities of tumor cells, polarization of M1 macrophages, and activation of T cells [26]. By amplifying the number of invading T cells in the inflammatory tumor microenvironment and boosting the responsiveness of immunotherapy, PAI diminishes the expression of microvessel density, catalyzes the growth of CD4+ T and CD8+ T lymphocytes, and suppresses the expression of VEGF [27]. Thus, the optimal therapeutic approach involves combining immunotherapy with anti-angiogenic therapy to attain a superior antitumor effect.

The present study revealed that the overall response rate of the combined use of PAI and endostar group was significantly higher than that of individual use of PAI or endostar. However, no significant differences were observed between the individual use of PAI and endostar. Fever was noted as the main adverse effect, occurring more frequently in the PAI combined with endostar group than the endostar group ($P < 0.05$). Nonetheless, the incidence of other toxic side effects was much less evident in the combined group compared to the individual use of PAI or endostar, suggesting that the combination treatment is comparatively superior in toxicity for the treatment of malignant pleural effusion and ascites. This decreased toxicity leads to better tolerability and patient compliance, ultimately resulting in improved treatment efficacy.

The present study, however, comes with some limitations. First, this was a retrospective study and the selection of patient as well as treatment assignments may be impacted by confounding factors. Second, the sample size was relatively small. Third, the patient survival results were not available for analysis.

Conclusion

The efficacy of PAI combined with endostar was determined to be noninferior to the effectiveness of either PAI or endostar in treating malignancy-induced malignant pleural effusion and ascites. Combining PAI and endostar also resulted in less toxicity when compared to using only PAI or endostar. These outcomes necessitate additional confirmation via well-designed prospective studies.

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Disclosure of conflict of interest

None.

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