A case of advanced lung cancer with malignant pericardial effusion treated by intrapericardial Cinobufacini injection instillation

Tao Sun, Yuhua Zhang, Yang Shen, Kaiwen Hu*, Minghuan Zuo*

Oncology Department, Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China.

Summary
Malignant pericardial effusion is one of the severe complications in advanced lung cancer patients, seriously affecting the patient's cardiopulmonary function and even life. Pericardial drainage and instillation of anti-neoplastic drugs in the pericardial cavity seems to offer the best chance of controlling pericardial effusion. We reported a case concerning treatment of a 63-year-old man in advanced lung cancer with a large amount of pericardial effusion. We utilized pericardium puncture and drainage combined with instillation of Cinobufacini injection in the pericardial cavity to treat pericardial effusion. After treatment with Cinobufacini injection for two weeks, the patient was followed up in one month to assess effectiveness, quality of life, and safety. We found that the cardiac tamponade symptoms such as difficult breathing, chest distress, and palpitations were significantly relieved. The patient's quality of life was effectively improved with KPS scores increased. We also found that the levels of tumor marker CA-125 in the pericardial effusion decreased (from 340.80 U/mL to 34.85 U/mL) and pericardium B ultrasound showed that the quantity of pericardial effusion reduced significantly (from 2.5 cm to 0.6 cm). Furthermore, there were little gastrointestinal adverse reactions and myelosuppression in the patient after instillation of the Cinobufacini injection. Taken together, this provides a new way for treating cancerous pericardial effusion, especially for patients who cannot tolerate instillation of chemotherapy drugs, and is worthwhile to carry out more standardized studies in the future.

Keywords: Cinobufacini injection, malignant pericardial effusion, advanced lung cancer, intrapericardial instillation

1. Introduction

Lung cancer is the leading cause of cancer-related mortality in men and women throughout the world and contributes approximately 1.37 million deaths per year worldwide (1). A series of complications occurs in advanced lung cancer, including malignant pleural effusion, pericardial effusion, central airway obstruction, and superior vena cava syndrome, which threatens life and necessitates urgent palliation (2). As one of the most common complications of advanced lung cancer, malignant pericardial effusion often leads to chronic cardiac tamponade and obstinate cardiac insufficiency, seriously affecting the patients' cardiopulmonary function and even life (3). Recently, various approaches have been proposed to prevent occurrence of pericardial effusion: extended drainage, pericardial window, sclerosing local therapy, local and/or systemic chemotherapy, and radiation therapy (4). For advanced lung cancer with pericardial effusion, pericardial drainage and the use of local anti-neoplastic therapy seems to offer the best chance of controlling effusion. Local instillation of anti-neoplastic agents (e.g., cisplatin) is used to cure the metastases rather than simply prevent effusion by drainage with short-term effective rates at 76-100% (5,6). Although local
instillation of chemotherapy is extremely effective, there are different levels of digestive tract, liver and kidney damage and blood toxicity reactions and other adverse reactions (6). Thus, it is urgent to look for novel anti-neoplastic agents to treat pericardial effusion. Recently, traditional Chinese medicines have attracted attention as candidates for treating malignant pericardial effusion opening a new research direction.

Cinobufacini injection or Huachansu injection, an aqueous extract from the skin and parotid venom glands of the toad (Bufo bufo gargarizans Cantor) that contains Chansu, is a Chinese medicine preparation widely used in clinical cancer therapy in China (7). Cinobufacini injection used alone or in combination with other chemotherapeutic agents (e.g., gemcitabine and oxaliplatin) have significant anticancer activity against many human cancers, such as non-small-cell lung cancer. It can improve the patients' quality of life and even effectively reduce tumor shrinkage with little toxicity (8). However, there are few reports about treating malignant pericardial effusion by instillation of Cinobufacini injection. In our department, pericardium puncture and pericardial cavity instillation of Cinobufacini injection using indwelling catheter drainage were performed for treating one advanced lung cancer patient with malignant pericardial effusion. The effect was satisfactory with good safety. Now the case report is presented as follows.

2. Case report

The patient was a 63-year-old man. Three years ago, he underwent a right lower pulmonary lobectomy because of lung space-occupying lesions according to CT examination results. The post-operative course was uneventful and pathology showed squamous carcinoma. After the operation, the patient received radiotherapy 30 times and six cycles of chemotherapy with regimens of gemcitabine with cisplatin, and the process of radiotherapy and chemotherapy went smoothly. Two years ago, the patient went to Cancer Institute & Hospital, Chinese Academy of Medical Sciences re-checking with chest CT examination and the results showed right side pleural effusion with a large amount of pericardial effusion and the heart B-ultrasound showed that the effusion had a length-diameter more than 2.0 cm (Note: the effusion quantity detected by echocardiography is commonly classified based on the method proposed by Dr. Weitzman (9), a small amount of effusion is defined as the maximum diastole dark space in the pericardial cavity < 1.0 cm while 1.0-1.9 cm for the medium amount of effusion, > 2.0 cm for a large amount of effusion). Furthermore, the level of CA-125 (340.80 U/mL) was extremely increased in the pericardial effusion. At the same time, no acid fast bacilli or toxic symptoms of TB were detected in pericardial effusion. Taken together, according to the patient's symptoms and signs and auxiliary examinations such as chest CT or pericardium B ultrasound, the diagnosis was clear: the patient showed phase IV advanced lung cancer with a large amount of pericardial effusion.

After being diagnosed, the patient was hospitalized in our department many times to improve pericardial effusion. First, the pericardium puncture was guided by ultrasonic probe positioning and a central venous catheter was indwelled for drainage. Briefly, after the puncture point was located by B ultrasound, the needle was inserted into the patient until the effusion was taken out and a guide wire was implanted slowly from the end of the needle puncture, and then the central venous catheter was entered into the pericardial cavity within 10 to 15 cm along with the guide wire, and finally the guide wire was pulled out and the central venous catheter was fixed for continuous drainage. Second, after drainage, the pericardium B ultrasound was performed to confirm if the pericardial effusion had completely drained out (the residual effusion in the pericardial cavity ≤ 0.2 cm), and then 40 mL of Cinobufacini injection was injected into the pericardial cavity. Finally, the catheter was closed and fastened, and the patient was advised repeatedly to change positions in order to ensure a maximum contact area between the drug and the inner pericardial cavity. Treatment took place twice per week with a course every two weeks. After treatment with a Cinobufacini injection course and one month later, the patient was followed up to assess effectiveness, quality of life, and safety. Furthermore, routine physical examinations, lab tests including blood routines, tumor markers in the pericardial effusion such as CA-125 and CEA, and morphologic imaging tests were performed during each follow-up. The response to Cinobufacini injection in treatment of malignant serous membrane cavity effusion was assessed using the WHO criteria (1979) as follows: (i) Complete response (CR): It was defined as effusion disappears entirely maintaining for at least 4 weeks according to clinical examination, chest radiography, CT or echocardiogram; (ii) Partial response (PR): It was defined as effusion reduced by more than 50% maintaining for at least 4 weeks; (iii) No remission (NR): It was defined as effusion beyond control or the effusion
Complications in advanced lung cancer patients. It
often affects circulatory and respiratory functions
rapidly causing difficulty in breathing, flustered,
shortness of breath, chest distress, cough, inability to
be supine, heart failure and even death. It seriously
affects the patient's survival and quality of life (3).
Thus, the immediate control of pericardial effusions
is mandatory for both survival and an improvement
in the performance status and the quality of life of patients. Pericardium puncture and drainage could
effectively relieve the above symptoms, however, if
only simple pericardial drainage is performed, effusion
currences can be observed in up to 40% of cases
(12). Instillation of cytotoxic chemotherapy drugs
in the pericardial cavity is most commonly used,
which can kill tumor cells directly and eliminate the
effusion. However, because of the limited efficacy of
existing chemotherapy drugs, obvious toxicity, and
easily relapsed malignant pericardial effusion, patient's
quality of life, treatment and prognosis are significantly
affected (13). Therefore, it is a big issue or challenge to
control the malignant pericardial effusion clinically and
an urgent need is to actively seek new efficient low-
toxicity drugs.

In recent years, many traditional Chinese medicines
have been shown to have potent anti-cancer effects
and have attracted considerable interest as potential
candidates for the development of novel cancer
therapeutics. Chansu is a traditional Chinese
treatment obtained from the post-auricular and skin glands of
Bufo bufo gargarizans Cantor, which has been used to
treat conditions like swelling, pain, and heart failure
for thousands of years in China and has recently
been used for treatment of cancer because of its anti-
cancer effects (14). Cinobufacini, a traditional Chinese
medicine containing the water-soluble components of
Chansu, exhibits a variety of biological activities, such
as anesthetic, anodyne, antimicrobial, cardioactive, and
antineoplastic properties (15). Currently, Cinobufacini
has been developed into a variety of dosage forms
such as tablets, oral solutions, and injections which

Table 1. The results of intrapericardial instillation of Cinobufacini injection for malignant pericardial effusion

<table>
<thead>
<tr>
<th>Items</th>
<th>Before Cinobufacini injection instillation</th>
<th>After Cinobufacini injection instillation one month later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Difficult breathing, chest distress, and palpitations</td>
<td>Difficult breathing relieved, no chest distress and palpitations</td>
</tr>
<tr>
<td>KPS scores</td>
<td>50 points</td>
<td>80 points</td>
</tr>
<tr>
<td>Blood routine</td>
<td>WBC: 7.36<em>10^5/L (N); RBC: 1.63</em>T/L (L); HGB: 55 g/L (L)</td>
<td>WBC: 6.51<em>10^5/L (N); RBC: 2.33</em>T/L (L); HGB: 85 g/L (L)</td>
</tr>
<tr>
<td>Tumor markers</td>
<td>CA-125: 340.80 U/mL (H); CEA: 2.07 ng/mL (N); NSE: 1.65 ng/mL (N)</td>
<td>CA-125: 34.85 U/mL (N); CEA: 2.25 ng/mL (N); NSE: 8.35 ng/mL (N)</td>
</tr>
<tr>
<td>Pericardium B ultrasound</td>
<td>Quantity of pericardial effusion: 2.5 cm</td>
<td>Quantity of pericardial effusion: 0.6 cm</td>
</tr>
</tbody>
</table>

Note: N means normal, L means low, and H means high.

quantity reduced less than 50% (10). The effectiveate was worked out by CR + PR. Quality of life was
assessed using Karnofsky performance scale (KPS)
scores with a score from 0 to 100, where 0 is dead
and 100 is completely normal (11). The safety profile
was assessed by recording: adverse events, physical
examinations, and lab and imaging tests.

The process of pericardium puncture was successful
and the patient did not experience any adverse effects
including complications of drainage insertion, or
infection with indwelling pericardial catheters after
puncture. Furthermore, the patient was steady without
any discomfort in the process of continuous drainage.
After Cinobufacini injection instillation, adverse
reactions such as pain, gastrointestinal reactions, shock,
infection, hemorrhage, arrythmia and pulse pause,
acute pulmonary edema and heart failure did not occur.

After treatment with Cinobufacini injection for two
weeks, the patient was followed up one month to assess
effectiveness, quality of life, and safety. The treatment
outcomes of the patient are summarized in Table 1.
The cardiac tamponade symptoms were significantly
relieved and symptoms such as difficult breathing, chest
distress, and palpitations were eased with KPS scores
increased to 80 points. Blood routine examinations
showed that there was no myelosuppression with
hemoglobin (HGB) increased from 55 g/L to 85 g/
L. The levels of tumor marker CA-125 in pericardial
effusion decreased from 340.80 U/mL to 34.85 U/
Ml and the levels of tumor marker CEA were normal.
Pericardium B ultrasound showed that the quantity
of pericardial effusion was significantly reduced. The
maximum diastole dark space in the pericardial cavity
decreased from 2.5 cm to 0.6 cm (Figure 1). That is
to say, that pericardial effusion was reduced by more
than 50% maintaining more than 4 weeks. The clinical
response to treatment was PR.

3. Discussion

Malignant pericardial effusion is one of the severe
complications in advanced lung cancer patients. It

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are approved by the Chinese State Food and Drug Administration (SFDA) and widely used to treat patients with lung, liver, colon, and pancreatic cancers at oncology clinics in China (7,8). It could effectively inhibit cell proliferation, induction of cell differentiation and apoptosis, disruption of the cell cycle, inhibition of cancer angiogenesis, reversal of multi-drug resistance, and regulation of the immune response in cancer cells (14). It also could effectively enhance physical immunity and improve the quality of life with little toxicity in cancer patients.

Recently, Cinobufacini injection has been reported to be effective for treating malignant pleural effusions and ascites. Zhang et al. found that symptoms such as cough, chest pain, difficult breathing, and chest distress were significantly relieved and the cancer patients’ quality of life was improved after intrapleural instillation of Cinobufacini injection with little gastrointestinal adverse reactions, myelosuppression and nephrotoxicity (16). Furthermore, Cinobufacini injection in combination with Cisplatin treating malignant pleural effusions by intrapleural instillation exhibited great synergistic action while improving efficiency and reducing the toxicity of Cisplatin (17). Ran reported that Cinobufacini injection in combination with BCG-polysaccharide nuceic acid treating malignant pleural effusions and ascites was effective for improving KPS scores with little adverse reaction (18). Taken together, instillation of Cinobufacini injection might be an effective therapy for malignant pleural effusions and ascites, especially for the patients who could not tolerate instillation of chemotherapy drugs. However, there are few reports on instillation of Cinobufacini injection treating malignant pericardial effusion. In the current study, we utilized pericardium puncture and drainage combined with instillation of Cinobufacini injection in the pericardial cavity to treat one advanced lung cancer patient with malignant pericardial effusion. The effect was satisfactory with good safety. We found that the cardiac tamponade symptoms such as difficult breathing, chest distress, and palpitations were significantly relieved after treatment with Cinobufacini injection. The patient’s quality of life was effectively improved with KPS scores increased. We also found that the levels of tumor marker CA-125 in pericardial effusion decreased and pericardium B ultrasound showed that the quantity of pericardial effusion was significantly reduced. Furthermore, there were little gastrointestinal adverse reactions and myelosuppression in the patient after instillation of Cinobufacini injection in the pericardial cavity.

To sum up, the current case report indicates that Cinobufacini injection instillation therapy is likely to become a new option for advanced lung cancer patients.

Figure 1. Quantitative assessment of pericardial effusion size in the patient was detected by pericardium B ultrasound, which was usually defined as the maximum diastole dark space in the pericardial cavity. (A) The quantity of pericardial effusion before pericardium puncture (2.5 cm); (B) The quantity of pericardial effusion after drainage (0 cm); (C) The quantity of pericardial effusion after instillation of Cinobufacini injections two weeks later (0.8 cm); (D) The quantity of pericardial effusion after instillation of Cinobufacini injections one month later (0.6 cm).
with malignant pericardial effusion. It is easy to perform with little adverse reactions. It can relieve the patient's suffering and improve quality of life. It provides a new way for treatment of cancerous pericardial effusion, especially for patients who cannot tolerate instillation of chemotherapy drugs, and it is worthwhile to carry out clinical observations using a larger group of patients and further standardized studies in the future.

Acknowledgements

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References


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