Chemical Pleurodesis Using Mistletoe Extraction (ABNOVAviscum® Injection) for Malignant Pleural Effusion

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Purpose: Malignant pleural effusion (MPE) is common in patients with advanced cancer. Chemical pleurodesis can be considered for MPE that do not respond to chemotherapy, radiotherapy, or therapeutic thoracentesis. However, it is not yet clear which agent is more effective and safer in chemical pleurodesis.

Methods: This study was designed as a single arm, multicenter, and open-label phase III clinical trial to evaluate efficacy and safety of chemical pleurodesis using mistletoe extraction (ABNOVAviscum® Injection). References of other agents in chemical pleurodesis were investigated to compare efficacy and safety. Efficacy was evaluated by followed up chest X-ray and changes of clinical symptoms and Karnofsky performance scale. Safety was evaluated by serious adverse event (SAE) and changes of laboratory findings. A follow-up period was 4 weeks after last pleurodesis.

Results: Of 62 patients, 49 (79.0%) had complete response, 11 (17.7%) had partial response, and two had no response. Mean response rate was significantly different in this study comparing with reference response rate which was 64% ($p < 0.0001$). There were two SAEs, but all were recovered without sequelas.

Conclusion: The results of this study suggest that mistletoe extraction (ABNOVAviscum® Injection) could be an effective and safe agent of chemical pleurodesis in patients with MPE.

Keywords: malignant pleural effusion, chemical pleurodesis, mistletoe extraction

Introduction

Malignant pleural effusion (MPE) is common in patients with advanced cancer and primary tumors are mainly lung cancer, breast cancer, lymphoma, ovarian cancer and gastric cancer. These malignancies account for 80% of all MPE1–5 and unknown origin MPE is about 10%.5,7 MPE are usually related to disseminate disease and median survival is from 3 to 12 months depending on cell type.5 Management for MPE is primarily focused on
the relief of symptoms and the prevention of recurrent pleural effusion. Of treatment modalities for MPE, chemical pleurodesis can be considered for MPE that do not respond to chemotherapy, radiotherapy, or therapeutic thoracentesis. But because the effect of chemical pleurodesis is different according to used agent, it is important to choose a more effective and safer agent in chemical pleurodesis. Although there are many reports about effective and safe chemical agent, it is not yet clear which is better. Of various agents, talc is known as a very effective agent however, small-particle talc could rarely develop acute respiratory distress syndrome. Unfortunately, large-particle talc known as safe agent for acute respiratory distress syndrome is not available in some countries including Korea. Bleomycin is less cost effective and tetracycline commonly used in the past is not available nowadays. Mistletoe extraction which is used in this study has been known as agent having anti-tumoral effect and immune modulation, but efficacy and safety of this agent in chemical pleurodesis for MPE need to be investigated.

**Materials and Methods**

This study was designed as a single arm, multicenter, and open-label phase III clinical trial to evaluate efficacy and safety of chemical pleurodesis using ABNOVAviscum® Injection (Abnoba GmbH, Germany), and was conducted in single-arm as the setting of the control group was not possible due to the lack of standard remedy for pleural effusions. Therefore, references of other agents in chemical pleurodesis were investigated to compare efficacy and safety and statistical sample size of study group was decided.

This study was carried out ethically and scientifically in accordance with Korea Good Clinical Practice (KGCP) and the Declaration of Helsinki. It was also conducted according to the approved protocol of Institutional Review Board (IRB) of Ministry of Food and Drug Safety (MFDS) and all institutions. After a full explanation, all patients participated in the study have signed the written informed consent form and all process and data of the study were audited by the monitor.

This study was sponsored by ABNOVA Korea and ABNOVA GmbH and there was no other funding agency’s role.

**Selection of study population**

**Inclusion criteria**

A. Male and female aged 20 to 80 years

B. Necessity of chemical pleurodesis among patients with MPE
   a. When repeated thoracostomy for MPE is needed
   b. Even though there is a persistent drainage of MPE during chest tube placement (>300 cc/day)

C. Full lung expansion must be achieved within 12 to 24 h after pleural drainage[9,9]

D. Expected survival of at least 2 months

E. Patients who score 50 or more on the Karnofsky performance scale (KPS)[10]

**Exclusion criteria**

A. Previous attempts at pleurodesis with sclerosing agents
B. Trapped lung or bronchial obstruction[9,11,12]
C. Adverse drug reactions to mistletoe agents
D. Patients having participated in another clinical study other than the present study
E. Patients taking immune-suppressive agents
F. Medical and psychiatric contraindications for the study drug
G. Not allowed to participate in the study by legal requirements
H. Not allowed to participate in the study by the Investigator’s judgment

**Treatments administered**

When pleural effusion was drained and the lung was confirmed of full expansion by a chest X-ray, treatment was performed. Treatment method is as below.

1. Remove the maximum amount of pleural fluid.
2. Mix five amples of ABNOVAviscum® F20mg Injection with 0.9% normal saline to inject the resulting mixture into the pleural space.
3. Determine a dosing interval (3 to 7 days) according to amounts of newly-generated pleural effusion and carry out the treatment until newly-generated pleural effusion has been resolved (<4 mm/kg/day).

**Measures of efficacy and safety data**

**Efficacy variables**

1. Primary efficacy
   The response rate (complete response (CR) and partial response (PR)) in pleural effusion were assessed as the primary efficacy variables by a simple X-ray examination at the close-out visit (4 weeks after the last pleurodesis).

   **Classification Criteria for Response Rate (WHO criteria)[13,14]**
   - Complete Response:
     Response with no replenishment of pleural effusion within 4 weeks after the last pleurodesis
• Partial Response:
  Response that does not need additional drainage
  since, in chest X-ray findings, there is the replenish-
  ment of pleural effusion under 50% of pleural effu-
  sion at the pre-treatment, but there are no symptoms
• No Response
  Response that needs additional treatment due to the
  recurrence of pleural effusion within 4 weeks after
  the last pleurodesis
• Not Evaluable

2. Secondary efficacy
Changes in clinical symptoms and KPS at the
pre-treatment and close-out visit were assessed as the
secondary efficacy variables.

Safety variables
The safety variables were adverse events newly
occurred after injecting the study drug and the results of
vital signs, physical examinations and clinical laboratory
tests performed at each visit.

Eligible patients: All patients who have had more
than one infusion of the investigational agent and of
whom the safety related data were verified by the inves-
tigator after the infusion.

1. Adverse Events
(1) Adverse Event (AE) means an undesirable and unin-
tended sign or symptom or disease which is occurred
in a patient during the study. An AE is not required
to the causal relation with the investigational agent.
(2) Serious adverse event (SAE) means one of the fol-
lowing AEs resulting from the investigational agent
used for the study:
  • death during the study period;
  • life-threatening;
  • persistent or significant disability or decreased
    function;
  • admission to hospital or lengthens the period of
    existing hospitalization;
  • congenital deformity or anomaly;
  • clinically important situation

2. Evaluation for other safety data
Liver function tests and kidney function tests at the
pre-treatment and close-out visit were performed to
observe changing aspects of liver and kidney functions.
And basic physical examinations including patient’s
height, weight, blood pressure and pulse were performed
to observe significant changes at the close-out visit com-
pared to the screening visit, and whether other special
changes occurred at the post-treatment by a questionnaire
survey was confirmed.

Statistical analysis methods
Analysis of primary efficacy variables was carried out
one sample binomial test for evaluating the response rate
(CR plus PR) in pleural effusion. 64% of hypothetical
proportion was used and a two-sided test was used.
For secondary efficacy variables, at less than 5% of sig-
nificance level, changes in the KPS using a paired t-test
were analyzed. SAS 9.3 was used for a statistical analy-
sis program.

Determination of subject size
The study was to evaluate the response rate in pleural
effusion by a simple chest X-ray test at close-out visit.
(1) Level of significance, $\alpha = 0.05$.
(2) Type II error ($\beta$) is 0.2 to maintain 80% of power of
  the test.
(3) Response rate of reference for other agents in chem-
  ical pleurodesis as 64% and AbnobaViscum®’s
  expected response rate of 81% were assumed
  from previous studies.
(4) The sample size was calculated by using the study
  size 2.0 program (Creostat HB 2001–2007).
  The calculated sample size is 56, and it was estimated
  that 68 patients were required considering 20% of drop-
  out rate.

Results
Characteristics of patients
68 patients were enrolled and, of them, 6 were dropped
out. The median age was 58 years old [range, 33–80 years]
and female was 39 (62.9%). The median duration of tumors
was 16 months [range, 1–227 months]. Divided by cate-
gory, ‘under 1 year’ was the highest with 41.9% (26/62
patients) followed by ‘1 to 2 years’ with 21.0% (13/62
patients), ‘2 to 3 years’ with 11.3% (7/62 patients) and oth-
ers with 25.8%. In the present metastasis state, the metas-
tasis was observed in 61 patients and most frequent in lung
with 37 patients (59.7%). The result of patients’ past med-
ical history showed 55 patients (88.7%) with medical his-
tory (total 226 cases). In detail, there were 47 cases (20.8%,
47/226) of ‘previous surgery’, 19 (8.4%) of ‘respiratory,
thoracic and mediastinal disorders’, 18 (8.0%) of ‘gastro-
intestinal disorders’, 17 (7.5%) of ‘infections’, and so on
(Table 1).

Characteristics of pleural effusion
The average duration of pleural effusion was 2.50
months [range, 1–21 months]. 36 patients (58.1%) had
pleural effusion on the right side, 22 (35.5%) on the left side and four (6.4%) on both sides. In the case with both sides, the right side which is the most severe site was selected for treatment. 41 patients (66.1%) had symptoms induced by the pleural effusion: dyspnea in 30 patients (48.4%, 30/62 patients); pleurodynia in 14 (22.6%), cough in seven (11.3%), loss of appetite in two (3.2%) and sleep disturbance in one (1.6%) (Table 2).

### Mistletoe-mediated pleurodesis

The dosing interval was determined according to the degree of pleural adhesion and the amount of the

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**Table 1** Characteristics of the patients at baseline

<table>
<thead>
<tr>
<th></th>
<th>n = 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>Median [range]</td>
</tr>
<tr>
<td>30 to 40 years</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>40 to 50 years</td>
<td>9 (14.5%)</td>
</tr>
<tr>
<td>50 to 60 years</td>
<td>20 (32.3%)</td>
</tr>
<tr>
<td>60 to 70 years</td>
<td>12 (19.4%)</td>
</tr>
<tr>
<td>Over 70 years</td>
<td>18 (29.0%)</td>
</tr>
<tr>
<td>Sex (n)</td>
<td>male:female 23:39</td>
</tr>
<tr>
<td>Primary cancer Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>28 (45.16%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>8 (12.9%)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1 (1.61%)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1 (1.61%)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>4 (6.45%)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1 (1.61%)</td>
</tr>
<tr>
<td>Papillary thyroid cancer</td>
<td>1 (1.61%)</td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>1 (1.61%)</td>
</tr>
<tr>
<td>Others</td>
<td>17 (27.41%)</td>
</tr>
<tr>
<td>Duration of tumors (month)</td>
<td>Median [range] 16.00 [1.0–227.0]</td>
</tr>
<tr>
<td>Under 1</td>
<td>26 (41.9%)</td>
</tr>
<tr>
<td>1 to 2</td>
<td>13 (21.0%)</td>
</tr>
<tr>
<td>2 to 3</td>
<td>7 (11.3%)</td>
</tr>
<tr>
<td>3 to 5</td>
<td>6 (9.6%)</td>
</tr>
<tr>
<td>5 to 10</td>
<td>5 (8.1%)</td>
</tr>
<tr>
<td>Over 10</td>
<td>5 (8.1%)</td>
</tr>
<tr>
<td>Present-metastasis state (n)</td>
<td>Existence:None 61:1 (98.4%:1.6%)</td>
</tr>
<tr>
<td>Past medical history (n)</td>
<td>Existence:None 55:7 (88.7%:11.3%)</td>
</tr>
</tbody>
</table>

**Table 2** Characteristics of pleural effusion

<table>
<thead>
<tr>
<th></th>
<th>n = 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pleural effusions (month)</td>
<td>Mean ± Std [range] 2.50 ± 4.25 [1.00–21.00]</td>
</tr>
<tr>
<td>Side of pleural effusions</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>36 (58.1%)</td>
</tr>
<tr>
<td>Left</td>
<td>22 (35.5%)</td>
</tr>
<tr>
<td>Both</td>
<td>4 (6.4%)</td>
</tr>
<tr>
<td>Symptoms related to pleural effusion</td>
<td>Presence:none 41:21 (66.1%:31.9%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>30 (48.4%)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (11.3%)</td>
</tr>
<tr>
<td>Pleurodynia</td>
<td>14 (22.6%)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>2 (3.2%)</td>
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</tbody>
</table>

n: number of patients
newly-generated pleural effusion, and the treatment was conducted until the pleural adhesion occurred. The pleural adhesion occurred mostly after one mistletoe-mediated pleurodesis. Looking at the actual number of treatment times, 50 patients (80.65%) had one pleurodesis, seven (11.29%) had 2, two patients (3.23%) each had 3 and 4, and one patient (1.61%) had 5 times. The average drainage duration and total amount of pleural effusion in the last pleurodesis was 6.27 days [range, 2–15 days] and 103.95 ml [range, 0–820 ml], respectively.

In the last pleurodesis, 33 patients (53.2%, 33/62) had no symptoms, 18 (29.0%) had pleurodynia, 12 (19.3%) had dyspnea, four (6.5%) had cough and two (3.2%, 2/62) had loss of appetite (Table 3).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Change of symptoms related to pleural effusion in the last pleurodesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 62)</td>
<td></td>
</tr>
<tr>
<td>No symptom</td>
<td>21 (31.9%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>30 (48.4%)</td>
</tr>
<tr>
<td>Cough</td>
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</tbody>
</table>

n: number of patients

Efficacy evaluation

(1) Primary efficacy variables

There were 49 CRs (79.03%), 11 PRs (17.74%), and 2 NRs (3.23%) out of the total 62 patients, resulting in overall response rate of 96.77% (60/62 patients). A binominal test for CR and PR was performed with a reference response rate of 64.0%. There was significant difference between the study and reference response rate (p < 0.0001).14,15

(2) Secondary efficacy variables

In the evaluation for change of clinical symptoms conducted at the close-out visit, 50 patients (80.7%, 50/62 patients) had no symptoms, 10 (16.1%) had dyspnea, two (3.2%) had pleurodynia, two (3.2%) had loss of appetite and one (1.6%) had cough (Fig. 1). And average changes in the KPS at the close-out visit compared to the screening visit were not statistically significant (1.48 ± 13.14%, p = 0.38).

Safety evaluation

AE means an undesirable and unintended sign or symptom or disease which is occurred in a patient during the study and an AE is not required to the causal relation with the investigational agent. During the conduct of the study, 309 cases AEs occurred in 61 out of the total 68 patients including six patients dropped out, resulting in 89.71% of incidence rate (IR). The most frequent AE was gastrointestinal disorders (25.89%, 80 cases). In detail, constipation (22 cases) was the most frequent AE, followed by nausea (17), dyspepsia (9), vomiting (9), and diarrhea (8). The second most frequent AE was general symptoms and localized symptoms around administration site (72 cases, 23.30%). In detail, pyrexia (39 cases) was the second most frequent AE, followed by pain (13) and chills (7). Of 309 cases, there were 42 cases AEs that cannot exclude casual relationship with the study drug in 27 patients (IR, 39.71%). Of these 42 cases of AEs, the most frequent AE was general symptoms and localized symptoms around administration site (32 cases, 76.19%). In detail, the most frequent AE was pyrexia (27), followed by chills (3), fatigue (1), and pain (1). These AEs were fully recovered. And two SAE that cannot exclude casual relationship with the study drug occurred in one patient (IR, 1.47%). A serious pleuritis and pain were included in SAE and recovered without sequela.

The changes of weight (p = 0.0001), systolic blood pressure (p = 0.0216), and pulse (p = 0.0008) were statistically significant, but not clinically significant. In a clinical laboratory test at the close-out visit compared to the screening visit, there were no significant changes in total bilirubin (p = 0.19), aspartate aminotransferase (AST) (p = 0.53), creatinine (p = 0.19), and blood urea nitrogen (BUN) (p = 0.52).

Discussion

An MPE is common in patients with advanced cancer and occurs as a result of obstruction of the pleural lymphatic drainage which results from the metastases of pleural and mediastinal lymph node in lung cancer, breast cancer, or gastric cancer. Although survival of patients with MPE is relatively poor, systemic chemotherapy, radiation treatment, or therapeutic thoracentesis have been attempted to treat MPE and the chemical pleurodesis can be considered for the patients who do not respond to above modalities. However, the effect of chemical pleurodesis is different according to used agent, so it is important to choose a more effective and safer agent in chemical pleurodesis. In this study, mistletoe extraction (ABNOVAviscum® Injection) was used as chemical agent for chemical pleurodesis in patients with MPE to investigate its therapeutic efficacy and safety, in order to overcome the problems of the existing agents. Mistletoe extraction (ABNOVAviscum® Injection)
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is known as an agent having anti-tumoral effect and immune modulation and has been used in some cancer patients in various ways. And the mechanism of mistletoe-mediated pleurodesis is known as stimulation of antitumor immunity rather than mechanical sclerosis.\(^{17}\)

The primary efficacy suggested in this study was response rate of mistletoe-mediated pleurodesis in MPE by a simple X-ray test at the close-out visit (4 weeks after the last pleurodesis), resulting in overall response rate of 96.77% (60/62 patients). In other words, mistletoe-mediated pleurodesis showed a higher response rate than other chemical pleurodesis in patients with MPE and there was significant difference between this study and a reference response rate (\(p<0.0001\)).\(^{14,15}\) The secondary efficacy variables were changes in clinical symptoms (dyspnea, cough, sleep disturbance, pain, etc.) and in the KPS at the pre-treatment and close-out visit. Several studies with other agents reported pleurodesis-related clinical symptoms were developed as chest pain (18% to 36%), fever (8% to 41%), nausea and vomiting (5%).\(^{18}\) In the evaluation for change of clinical symptoms conducted at the close-out visit, it was investigated that 50 patients (80.65%, 50/62 patients) had no symptoms. In other words, the proportion of patients without symptom was increased from 31.9% to 80.7%, and the proportion of dyspnea, cough, and pleurodynia was decreased from 48.4% to 16.1%, from 11.3% to 1.6%, and from 22.6% to 3.2%, respectively (Fig. 1). This suggests that clinical symptoms tended to be improved after mistletoe-mediated pleurodesis. There was no significant improvement in KPS at the close-out visit, but this might be interpreted as few damage of mistletoe-mediated pleurodesis itself to patients.

The safety variables assessed in this study were AEs and change in physical measurements and vital signs and laboratory test at the pre-treatment and post-treatment. In this study, of the total 309 cases AEs, there were 42 cases AEs that cannot exclude casual relationship with the study drug and, of 42 cases, the most frequent AE was pyrexia. Comparing the occurred AEs to the existing drug safety profile of AbnobaViscum\(^{®}\) Injection, we confirmed

**Fig. 1** Change of symptoms related to pleural effusion at the close-out visit. In the evaluation for change of clinical symptoms conducted at the close-out visit, the proportion of patients without symptom was increased from 31.9% to 80.7%, and the proportion of dyspnea, cough, and pleurodynia was decreased from 48.4% to 16.1%, from 11.3% to 1.6%, and from 22.6% to 3.2%, respectively.
that pyrexia of 32.35% out of the total 68 patients was an expectable AE and that pyrexia occurred due to an infusion of ABNOVAViscum® Injection does not need to be treated with an antifebrile, because pleural inflammation is a therapeutic response generating in the mechanism of pleural adhesion and is known to cause the adhesion.\textsuperscript{19,20} Although antibiotics were administrated to the concerned patients to treat the inflammation caused by elevation of inflammatory factors (creative protien (CRP) etc.), the elevation of the inflammatory factors (white blood cell (WBC), erythrocyte sedimentation rate (ESR), CRP etc.) after the pleurodesis is an expected response, hence it is advised not to administer antibiotics.\textsuperscript{21} The two cases of SAE mentioned in results recovered without sequel. The changes in height, weight, blood pressure and pulse at the close-out visit compared to the screening visit were statistically significant, but these changes were not clinically significant. There were no significant changes in clinical laboratory tests performed at the close-out visit compared to the screening visit.

**Conclusion**

The results of this study suggest that mistletoe extraction (ABNOVAViscum® Injection) could be an effective and safe agent of chemical pleurodesis in patients with MPE.

**Disclosure Statement**

This study was granted by Abnoba Korea and Abnoba GmbH and it was presented at the 15th World Conference on Lung cancer in 2013.

**References**


