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ORIGINAL ARTICLE

Efficacy and safety of *Viscum album* extract (Helixor-M) to treat malignant pleural effusion in patients with lung cancer

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Abstract

Purpose Manifestations of malignant pleural effusions (MPEs) are alleviated by local therapies as well as by systemic treatment. After 2009, when commercial use of talc was discontinued in Korea, we have used Helixor-M, which is derived from the European mistletoe (*Viscum album*), as an alternative sclerosing agent for pleurodesis. We aimed to evaluate the efficacy and safety of Helixor-M for controlling MPE.

Methods Between 2009 and 2015, we consecutively enrolled 52 patients with lung cancer, who underwent pleurodesis to treat MPE and were analyzed retrospectively. On day 1, 100 mg of Helixor-M was instilled via pleural catheter. If the procedure was not effective, it was repeated every other day up to five times, and the dose increased each time by 100 mg. The primary study outcome was reappearance of pleural effusion at 1 month after the last pleurodesis procedure.

Results The median age of patient was 63 years, and 77% of the 52 patients were male. About 85% of pleural effusions were found to be malignant by cytogenetic analysis. Forty-two (81%) patients were evaluable for recurrence of MPE. The 1-month recurrence rate was 48% (20/42). Among the 20 patients who developed recurrent MPE, 6 required therapeutic thoracentesis. Thirteen (25%) patients experienced procedure-related pain requiring medication. Eight (15%) had fever > 38 °C.

Conclusions Our results suggest that a pleurodesis with Helixor-M was an effective and tolerable procedure for controlling MPE in lung cancer patients.

Keywords Malignant pleural effusion · Pleurodesis · *Viscum album*

Introduction

Lung cancer, the most common metastatic tumor to the pleura, accounts for approximately 40% of all malignant pleural effusions (MPEs) [1]. Management of asymptomatic MPE can be deferred until the development of symptoms. However, most MPEs eventually become symptomatic. Patients with symptomatic MPE undergo therapeutic thoracentesis to relieve respiratory symptoms and for evaluation of the etiology. Because symptomatic MPEs may not respond to systemic treatment for the underlying lung cancer, they require local palliative therapy directed at the pleural space, which includes pleurodesis.

Talc is known for the most effective sclerosant of choice for pleurodesis [2]. However, talc pleurodesis has serious safety concerns, including acute respiratory failure and acute respiratory distress syndrome [3–5]. Furthermore, in 2009, talc use was discontinued in Republic of Korea because some commercial products containing talcum powder were reported to contain asbestos, which is a well known carcinogen that can cause malignant mesothelioma.

Mistletoe is a semiparasitic plant that grows on various species of host trees. An extract from *Viscum album*, a European mistletoe, is one of the commonly prescribed anticancer adjuvant treatments mainly in Europe and Republic of Korea for stimulating the immune system [6–8]. *Viscum album* extract has also been used for chemical pleurodesis to treat MPEs. A small preliminary study of the intrapleural instillation of *V. album* extract for 20 patients with MPE found an overall response rate of 72%, minimal side effects [9].

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Subsequent research revealed that the response to mistletoe-mediated pleurodesis is the result of stimulation of antitumor immunity rather than mechanical sclerosis [9].

Helixor-M (made by Helixor Heilmittel GmbH & Co. KG, Germany), an aqueous solution of *V. album* extract, is among the commonly used unconventional remedies in Republic of Korea. This study aimed to evaluate the efficacy and safety of Helixor-M as a sclerosing agent for pleurodesis that was performed to control MPE in lung cancer patients.

Methods

Patients

All patients who were diagnosed with lung cancer and treated with Helixor-M for MPE between May 2009 and April 2015 at Kangbuk Samsung Hospital were included and analyzed retrospectively. Basically, the diagnosis of MPE was established by cytological proof of pleural malignancy. If a patient appears to have a MPE clinically but cytologic examination of pleural fluids does not find malignant cells, a cytologically not proven but clinically MPE must meet the following criteria: (1) histopathologically proven malignancy at the primary site, (2) exudative pleural effusions according to Light's criteria [10], (3) no evidence of microbiological infection, and (4) the reappearance of a large pleural effusion without treatment. After providing written informed consent, each patient underwent Helixor-M pleurodesis. This study was approved by our institutional review board (No. KBSMC 2016–07-045).

Protocol of chemical pleurodesis with Helixor-M

A 12F intercostal catheter was initially inserted percutaneously, with the hospitalized study patient under ultrasonographic guidance. A large volume of malignant pleural fluid of up to 1 L/day was drained from the patient, and the specimen was prepared for cytological examination by a cell block method. Drainage of malignant pleural fluid continued until the volume was reduced to less than 100 mL/day. After radiological confirmation of the complete re-expansion of the affected lung and confirmation of the position of the intercostal catheter, the patients were received the informed consents form for pleurodesis. Helixor-M (100 mg) was then instilled into the pleural space via the intercostal catheter, and the tube was clamped. The patient was then rotated over a 3-h period to achieve adequate distribution of the Helixor-M over the pleura. If the drainage volume remained greater than 50 mL/day, the procedure was repeated up to five times every other day with a 100-mg increase in the dose of Helixor-M for each subsequent procedure [11]. All enrolled study patients were treated for the primary tumor according to standard-of-care guidelines and oncological advice.

Study outcomes and statistical analysis

The primary study outcome was the radiological reappearance of MPE at 1 month after the last pleurodesis procedure, as assessed by chest X-ray on a decubitus view. Toxicity was assessed in accordance with the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Multivariate logistic regression analysis was used to investigate independent predictors of the successful Helixor-M pleurodesis. Variables with a P value ≤ 0.05 were considered significant. Statistical analysis was performed by Stata 13.0 software (Stata Corp LP, College Station, TX, USA).

Results

Patient characteristics

The baseline characteristics of patients are summarized in Table 1. A total of 52 patients with advanced lung cancer and MPE underwent Helixor-M pleurodesis. The median age was 63 years (range, 57–71 years), and 77% of patients were male. The most common histopathology was adenocarcinoma in 36 (69%) patients, followed by squamous cell carcinoma in 7 (13%), non-small-cell lung cancer not otherwise specified in 5 (10%), and small-cell lung cancer in 4 (8%). Among 52 patients, 44 (85%) were proven to have MPE by cytological analyses. The other eight (15%) patients were diagnosed to have MPE by the reappearance of a large pleural effusion in the context of pathologically proven malignancy at the primary site. All of eight pleural effusions were characterized by lymphocytes dominant exudates and were not related to infections. To identify the presence of malignant cells, we repeated cytogenetical analyses at least two times but failed to find any malignant cells in these eight cases. MPE was located in the right lung of 65% of patients, in the left lung of 25%, and bilaterally in 10%. The characteristics of pleural effusion were summarized in Table 2.

At the time of pleurodesis, 26 (50%) patients were naïve for systemic treatment, and the others had received systemic therapy.

Study outcome

Among 52 patients, 42 (81%) were evaluable for reappearance of MPE. Study outcomes and adverse events are summarized in Table 3. Ten (19%) patients were not evaluable because 7 patients died for disease progression within 30 days after the procedure, and 3 patients were lost to follow-up. Of 42 evaluable patients, the 1-month reappearance rate was 48% (20/42) (95%

Table 1 Baseline characteristics of study patients ($n = 52$)

Characteristics	Number (%)
Median age (years)	63 (57–71, interquartile range)
Gender	
Male	40 (77)
Female	12 (23)
ECOG performance status	
1	35 (67)
2	11 (21)
3	6 (12)
Histopathology	
Adenocarcinoma	36 (69)
Squamous cell carcinoma	7 (13)
Non-small cell, not otherwise specified	5 (10)
Small-cell carcinoma	4 (8)
EGFR mutation ($n = 46$, excluding small cell)	
Sensitizing mutation	11 (24)
Wild type	35 (76)
Systemic treatment	
Treatment naïve	26 (50)
Prior systemic treatment	26 (50)

ECOG Eastern Cooperative Oncology Group, EGFR epidermal growth factor receptor

confidence interval [CI], 32–63%). Among 20 patients who showed reappearance of MPE, 6 required a therapeutic thoracentesis. The recurrence rate was 35% (7/20) in systemic-treatment-naïve patients and 59% (13/22) in non-naïve patients. When the analysis was performed on the response of chemotherapy administered at the time of pleurodesis, the recurrence rate was 46% (12/26) in patients who responded to chemotherapy, whereas the recurrence rate was 58% (7/12) in patients who did not respond to subsequent chemotherapy.

Table 2 Characteristics of pleural effusion

Characteristics	Number (%)
Location	
Left	13 (25)
Right	34 (65)
Bilateral	5 (10)
Pleural fluid cytology for malignancy	
Not confirmed	8 (15)
Confirmed	44 (85)
Chemistry	Median [range]
pH	7.2 [7–7.8]
LDH (U/L)	477 [130–3072]
Albumin (g/dL)	2.7 [1.7–4.1]
Glucose (mg/dL)	103 [1–239]

LDH lactate dehydrogenase

The study patients received a median of three instillations of Helixor-M for pleurodesis (range, 1–5). Six patients had received five instillation (maximum) of Helixor-M pleurodesis. Of these six patients, two patients were refractory cases, which did not respond to maximum procedure of Helixor-M pleurodesis.

Toxicity

The most common procedure-related toxicity was pain. Of all 52 patients, 13 (25%) complained of pleurodesis-related pain, which required pain medication. About 15% of patients developed fever greater than 38 °C, and 12% required increased oxygen. Only 2 (4%) patients were found to have pneumothorax after pleurodesis.

Univariate and multivariate analyses for the success of Helixor-M pleurodesis

By univariate and multivariate analyses, none of the patients' characteristics, including age, gender, histopathology, systemic treatment, and none of the MPE characteristics, including location and chemistry, were significantly associated with the outcome of Helixor-M pleurodesis (Table 4).

Discussion

The aim of this study was to evaluate the efficacy and safety of Helixor-M pleurodesis for managing MPE in patients with advanced lung cancer. Helixor-M pleurodesis successfully prevented recurrence of pleural effusion at 1 month after pleurodesis in about 52% of 42 patients with MPE. Pain that required medication affected 25% of patients, and about 15% of patients developed fever.

Current guidelines recommend talc as the preferred sclerosant for pleurodesis [1]. The success rate of talc for

Table 3 Study outcomes and adverse events after Helixor-M pleurodesis

Outcomes	Number (%)
Reappearance of effusion at 1 month after pleurodesis[a]	
No	22 (52%)
Yes	20 (48%)
Adverse events	
Pain requiring pain medication	13 (25%)
Fever over 38 °C	8 (15%)
Increase in oxygen demand	6 (12%)
2003Pneumothorax	2 (4%)

[a] Among 52 patients who received Helixor-M pleurodesis, 42 patients were evaluable for efficacy

Table 4 Univariate and multivariate analyses for recurrence of malignant pleural effusion in 42 evaluable patients who underwent Helixor M pleurodesis

Characteristics	Univariate		Multivariate	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Age (years)				
> 63 vs. ≤ 63	0.56 (0.16–1.89)	0.348	0.61 (0.16–2.36)	0.470
Gender				
Male vs. female	1.5 (0.35–6.35)	0.582	1.92 (0.37–9.91)	0.435
Histology				
Squamous	1.0[a]		1.0[a]	
Non-squamous	0.88 (0.15–5.05)	0.888	0.79 (0.13–5.02)	0.805
Small-cell lung cancer	1.00 (0.08–12.56)	1.000	0.46 (0.03–7.25)	0.584
Systemic treatment				
Prior treatment	1.0[a]		1.0[a]	
Treatment naïve	0.37 (0.11–1.30)	0.145	0.35 (0.09–1.44)	0.146
Location of pleural effusion				
Left	1.0[a]		1.0[a]	
Right	0.67 (0.16–2.73)	0.573	0.51 (0.11–2.33)	0.384
Both	0.83 (0.08–8.24)	0.876	0.49 (0.04–6.73)	0.597
Chemistry				
pH (> 7.2 vs. ≤ 7.2)	1.27 (0.30–5.33)	0.741	0.44 (0.02–9.92)	0.606
LDH (> 477 vs. ≤ 477)	1.57 (0.42–5.90)	0.503	1.68 (0.12–24.45)	0.704
Albumin (> 2.7 vs. ≤ 2.7)	0.36 (0.08–1.64)	0.188	0.30 (0.03–3.38)	0.328
Glucose (> 103 vs. ≤ 103)	0.88 (0.23–3.34)	0.845	0.13 (0.01–2.94)	0.201

LDH lactate dehydrogenase

[a] Reference

preventing reappearance of MPE ranges from 60 to 90%, which is superior to the outcomes obtained by other agents (i.e., bleomycin, tetracycline, mustine) [2, 12–15]. However, there are safety concerns with talc pleurodesis; studies have reported that 1 to 9% of patients treated with talc develop serious pulmonary complications such as respiratory failure and acute respiratory distress syndrome [3–5]. A more recent large prospective observational study found that the size of a talc particle was associated with risk of respiratory complications, and that large-particle talc for pleurodesis was not associated with serious respiratory complications [16]. In our study, Helixor-M pleurodesis achieved a 52% of success rate for controlling recurrent MPE. Although our data did not show results superior to talc pleurodesis, the results of Helixor-M pleurodesis were comparable to those of pleurodesis using other agents, including bleomycin and tetracycline [17]. Therefore, under circumstances where commercial talc is not available, Helixor-M pleurodesis could be a reasonable alternative for controlling MPE in patients with lung cancer. Most detectable adverse effects were manageable by agents for relieving signs and symptoms, which included pain and fever. Since our protocol for Helixor-M pleurodesis did not include pain prophylaxis, we might have decreased the severity of pain if we had incorporated pain premedication into the protocol.

The precise mechanism of action of Helixor-M pleurodesis remains poorly understood. Stumpf et al. reported that intrapleural instillation of mistletoe extract stimulated antitumor immunity by increasing the number of lymphocytes and reducing the number of malignant cells in pleural fluid [9]. We presume that both an inflammatory reaction involving the visceral and parietal pleura and antitumor activity via nonspecific immune activation contributed to the outcome of Helixor-M pleurodesis in our study.

Our data showed that the response to Helixor-M pleurodesis was independent of age, gender, lung cancer histopathology, systemic treatment, and characteristics of pleural fluid [18]. The recurrence rate of pleurodesis for treatment-naïve patients was lower than the recurrence rate for non-naïve patients. In chemotherapy-naïve patients, MPE was detected at the right time of lung cancer diagnosis. Therefore, systemic therapy started around the same time of Helixor-M pleurodesis. On the other hand, in chemotherapy-pretreated patients, MPE was developed after failure of chemotherapy. Given the lower response rate of second or later line of chemotherapy, chemotherapy-pretreated patients were less likely to be affected by subsequent therapy. In our analyses, the recurrence rate of pleurodesis for chemotherapy responders was lower than the response rate for chemotherapy non-responders. These can explain the difference in recurrence rates

between treatment-naïve and non-naïve patients, though it was not statistically significant ($P = 0.118$). The induction of nonspecific pleural inflammation and fibrosis by Helixor-M can partly explain the absence of predictive markers for the success of chemical pleurodesis.

Our findings are limited by selection bias due to the retrospective design of the study and small sample. Furthermore, a retrospective review of medical records might have led to an underestimation of patient-reported adverse events, which might not have been recorded. In case of seven patients who died within 30 days after Helixor-M pleurodesis, we have concluded that the cause of death is not related to the procedure but to disease progression. However, for some patients, it was not possible to completely exclude the association with the treatment. For the diagnosis of MPE, we included eight patients who had pleural effusions in the absence of malignant cells by cytology, but who were suspected of "malignant" effusions in the presence of repeated accumulation of symptomatic pleural effusion characterized by lymphocyte dominant exudate. All eight patients did not have evidence of microbacterial infection. Given cytology is the gold standard method for the diagnosis of MPE, there is the possibility that the study population may include patients who do not really have MPE. However, this study does show the efficacy of the Helixor-M sclerosant used as an alternative to talc. Since many investigators have concerns about the scientific validity of the evidence of the efficacy of mistletoe extracts [19], we hope that our results might be a contribution to the scientific evidence for an adjunctive role of the mistletoe extracts, Helixor-M, as a pleurodesis sclerosant.

In conclusion, Helixor-M pleurodesis was an effective and tolerable procedure for controlling MPE in lung cancer patients. Under circumstances where commercial talc is unavailable for use as a sclerosant, as in Republic of Korea, we believe that we can consider Helixor-M as an alternative sclerosant for pleurodesis. Additional large prospective trials are warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Kangbuk Samsung Hospital Institutional Review Board (No. KBSMC 2016–07-045) and with the 1964 Declaration of Helsinki and its later amendments.

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