Risk Factors for Chest Pain and Fever in Patients Undergoing Pleurodesis with OK-432

Yoshihito Morimoto 1, Hidefumi Takei 1, Keisei Tachibana 2, Yoko Nakazato 1, Ryota Tanaka 2, Yasushi Nagashima 2, Kazuhiro Watanabe 1, Reisuke Seki 1, Takao Shinohara 3 and Haruhiko Kondo 2

Abstract:
Objective: In Japan, pleurodesis is often performed using OK-432. However, OK-432 may cause severe chest pain and fever. The risk factors for these complications are unclear. The aim of this study was to identify the risk factors for chest pain and fever caused by pleurodesis with OK-432.

Methods: The clinical data of 94 patients who underwent pleurodesis with OK-432 were retrospectively analyzed. Patients who developed chest pain (indicated by a record of rescue pain medication) and/or fever (a recorded temperature of >38°C) were identified. A logistic regression analysis was performed to determine the risk factors for these complications.

Results: Rescue medication for chest pain was required by 43.6% of the patients and 40.4% developed pyrexia after pleurodesis with OK-432. The univariate analysis showed that the likelihood of requiring rescue medication for chest pain was significantly increased in patients of <70 years of age (p=0.028) and in those who were not premedicated with a nonsteroidal anti-inflammatory drug (NSAID; p=0.003). Age <70 years (adjusted odds ratio 2.97, 95% confidence interval 1.10-8.00, p=0.031) and a lack of premedication with an NSAID (adjusted odds ratio 4.21, 95% confidence interval 1.47-12.04, p=0.007) remained significant factors in a multivariate analysis. The absence of NSAID premedication was the only statistically significant risk factor for fever in the univariate analysis (p=0.034). The multivariate analysis revealed no significant risk factors for fever.

Conclusion: The results of the present study suggest that premedication with an NSAID might be useful for preventing the chest pain caused by pleurodesis with OK-432. Furthermore, caution is advised when managing chest pain in adults of <70 years of age. Prospective studies should be performed to further investigate this issue.

Key words: OK-432, pleurodesis, chest pain, fever, risk factors

(Intern Med Advance Publication)
(DOI: 10.2169/internalmedicine.9637-17)

Introduction

Pleurodesis is commonly performed in the treatment of patients with malignant pleural effusion, complications after lung surgery, and pneumothorax. The procedure entails the introduction of a sclerosing agent into the pleural space to cause inflammation and the obliteration of the space between the visceral and parietal pleura. OK-432 (a purified preparation derived from Streptococcus pyogenes) is commonly used as a sclerosing agent in Japan. Several studies have shown that OK-432 is useful for pleurodesis (1-3). In Western countries, talc has been the gold standard sclerosing agent for pleurodesis for many years. Talc was approved for pleurodesis in Japan in December 2013, but only for patients with malignant pleural effusion. Thus, OK-432 is a...
well-established agent that has been conventionally used for patients with malignant pleural effusion, postoperative complications, and pneumothorax. However, pleurodesis using OK-432 is associated with complications, particularly chest pain and fever (1, 4), the reasons for which have not been clarified. The aim of this study was to identify the risk factors for complications in patients undergoing pleurodesis with OK-432.

### Materials and Methods

#### Patients

We retrospectively reviewed the medical records in the Department of General Thoracic Surgery, Kyorin University Hospital, and identified 97 potential study participants who had undergone pleurodesis with OK-432 between February 2013 and July 2016. Three patients were excluded (the volume of OK-432 was unclear in two patients and the body height was not measured in 1 patient); thus, the data of 94 patients were available for the analysis. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of Kyorin University Hospital (approval number: 776).

#### Procedure

In all cases, OK-432 (Picibanil, Chugai Pharmaceutical Co Ltd, Tokyo, Japan) was injected into the pleural space via a 16-24 Fr chest tube connected to a water-sealed drainage system. OK-432 was administered at a dose of 5 KE or 10 KE (Klinische Einheit; 1 KE contains 0.1 mg of dried cocci). Two hundred milligrams of minocycline and lidocaine 1% could also be administered at the discretion of the attending physician. These drugs were suspended in 20-100 mL of saline or autologous blood. Lidocaine (1%) was administered at the same time or just prior to the administration of OK-432. The physician also determined the position of the patient in bed. The analgesic agents used before pleurodesis varied from patient to patient.

#### Evaluation

Chest pain was defined as the need for rescue pain medication and fever was defined as a body temperature of >38°C after pleurodesis. Fever was evaluated in accordance with the National Cancer Institute Common Terminology Criteria version 4.0.

#### The risk factors for chest pain and fever

The following demographic and clinical variables were investigated to determine their relationship with chest pain and fever after pleurodesis with OK-432. The variables were divided into two groups based on the approximate median values: age (<70 or ≥70 years), sex (male or female), body height (≥160 or <160 cm), body weight (≥55 or <55 kg), body surface area (≥1.6 or <1.6 m²), disease (malignant pleural effusion or not), albumin (≥3.2 or <3.2 g/dL), C-reactive protein (≥3.0 or <3.0 mg/dL), 24-h drainage volume on the day before pleurodesis (≥150 or <150 mL), dose of OK-432 (10 or 5 KE), administration of minocycline (yes/no), administration of autologous blood (yes/no), volume of solution (100 or ≤50 mL), administration of lidocaine (1%; yes/no), and premedication with an NSAID, acetaminophen, and/or opioid (yes/no).

### Statistical analysis

Potential risk factors for chest pain and fever caused by pleurodesis with OK-432 were tested by a logistic regression analysis. Factors with an odds ratio <0.5 or >2.0 in the univariate analysis were included in a multivariate analysis. All of the statistical analyses were performed using the StatView software program (version 5 for Windows, SAS Institute, Cary, NC). P values of <0.05 were considered to indicate statistical significance.

#### Results

#### Patients

The clinical and demographic characteristics of the 94 patients (male, n=63; female, n=31) who underwent pleurodesis with OK-432 are shown in Table 1. Forty-five of these patients had malignant pleural effusion, 27 had postoperative complications, and 22 had pneumothorax. All 27 postoperative patients had undergone pulmonary tumor resection by video-assisted thoracic surgery. Eighty-four patients (89.4%) received OK-432 at a dose of 10 KE, and 10 (10.6%) received OK-432 at a dose of 5 KE. Eleven patients (11.7%) also received minocycline (200 mg). Forty-eight patients (51.1%) received lidocaine (1%), the volume of which was 10 mL in 41 patients, 20 mL in 5 patients, and unknown in 2 patients. For pain relief, 66 patients (70.2%) were premedicated with an NSAID, 22 with acetaminophen (23.4%) and 29 with an opioid (30.9%). The NSAIDs included loxoprofen (60 mg, orally, thrice daily; n=61, 92.4%) or celecoxib (200 mg or 400 mg, orally, once daily; n=5, 7.6%). Various acetaminophen and opioid regimens were used. Acetaminophen was administered orally at a dose of 325-1,600 mg per day. The daily acetaminophen doses were 1,600 mg for 2 patients; 1,300 mg for 13 patients; 1,200, 975, and 650 mg for 1 patient each; 325 mg for 2 patients; and unknown for 2 patients. The opioids prescribed included tramadol, oxycodone, morphine, and fentanyl. The most commonly used opioid was tramadol (150 mg, daily), which was administered to 19 patients.

#### The complications of pleurodesis

The complications of pleurodesis with OK-432 are shown in Table 2. Forty-one patients (43.6%) required rescue medication for chest pain, which was usually an NSAID (in 58.5% of cases), and which was most often diclofenac (50 mg, by suppository). Thirty-eight patients (40.4%) developed fever, which was graded as <3 in all cases.
The risk factors for needing rescue medication to treat OK-432-related chest pain and fever

Among the clinical factors that were entered in the univariate analysis, age <70 years and no premedication with an NSAID were statistically significant predictors of the need for rescue medication to manage pleurodesis-related chest pain (p=0.028 and p=0.003, respectively; Table 3). No use of lidocaine (1%) and no premedication with acetaminophen or an opioid were not significant risk factors.

In the multivariate analysis, age <70 years, and no premedication with an NSAID were statistically significant predictors of the need for rescue medication to manage pleurodesis-related chest pain (adjusted odds ratio 2.43, 95% confidence interval 0.95-6.22, p=0.065).

Discussion

To date, there have been no reports on the risk factors for complications of pleurodesis using OK-432. In the present study, we made some important clinical observations. In particular, age <70 years and the absence of premedication with an NSAID were statistically significant predictors of the need for rescue medication to manage chest pain.

The mechanism of the therapeutic effects of OK-432 for malignant effusion is thought to involve the induction of the release of various inflammatory cytokines, such as tumor necrosis factor-α, interferon-γ, interleukin-1, and interleukin-8, which cause the fusion of the parietal and visceral pleurae; however, it is associated with an increased risk of adverse effects (chest pain and fever) from severe pleuritis. In this study, the rates of chest pain and fever due to pleurodesis with OK-432 were 43.6% and 40.4% respectively. This is consistent with previous reports (1, 4).

Chest pain was less common in elderly adults (≥70 years) than in their younger adult counterparts (<70 years). It is known that the immune response decreases with increasing age. Age-associated changes in the signal transduction and function of neutrophils and in the development and function of lymphocytes have been reported (7, 8). Given our finding that chest pain was less common in elderly adults, it may be that the inflammation triggered by the immune response to pleurodesis with OK-432 is milder in that age group. Fever was also less common in elderly adults; albeit, not significantly so.

The absence of premedication with an NSAID was a significant predictor of the need for rescue medication to manage chest pain. There is no consensus on the use of premedication for pleurodesis (9). Animal studies have shown that NSAIDs may impair the action of agents used for pleurodesis (10). Thus, there is a widespread belief that

Table 1. Patient Clinical and Demographic Characteristics (n=94).

| Patients (n) |
|----------------|
| Median age, years (range) | 68.5 (23-91) |
| Sex Male/Female | 63/31 |
| Median body height, cm (range) | 161.2 (143.3-175.8) |
| Median body weight, kg (range) | 54 (32.3-89.9) |
| Median body surface area m² (range) | 1.56 (1.172-1.984) |
| Disease |
| Malignant pleural effusion | 45 |
| Complication of lung surgery | 27 |
| Pneumothorax | 22 |
| Median albumin, g/dL (range) | 3.2 (1.5-4.7) |
| Median C-reactive protein, mg/dL (range) | 3.1 (0.1-21.6) |
| Median 24-h drainage volume on the day before pleurodesis, mL (range) | 155 (0-2,300) |
| Dose of OK-432 |
| 10 KE/5 KE | 84/10 |
| Administration of minocycline |
| Yes/No | 11/83 |
| Administration of lidocaine 1% |
| Yes/No | 48/46 |
| Administration of autologous blood |
| Yes/No | 13/81 |
| Volume of solution |
| ≤50 mL/100 mL | 43/51 |
| Analgesic premedication |
| NSAID Yes/No | 66/28 |
| Acetaminophen Yes/No | 22/72 |
| Opioid Yes/No | 29/65 |

KE: Klinische Einheit, NSAID: nonsteroidal anti-inflammatory drug

Table 2. Complications of Pleurodesis.

| Rescue medicine for chest pain, n (%) | 41 (43.6) |
| Rescue medicine |
| NSAID | 24 |
| Acetaminophen | 6 |
| Opioid and acetaminophen | 5 |
| Opioid | 4 |
| Pentazocine | 2 |
| Fever, n (%) | 38 (40.4) |
| Grade 1 | 29 |
| Grade 2 | 9 |
| Grade 3 | 0 |

NSAID: nonsteroidal anti-inflammatory drug
NSAIDs should be avoided before the procedure. A multi-center randomized trial (TIME1) that compared the effects of opioids versus NSAIDs and larger versus smaller chest tube sizes on pain control in patients undergoing talc pleurodesis for malignant pleural effusion found that there was no significant difference in the pain scores of patients premedicated with NSAIDs or opiates and that the efficacy of pleurodesis at 3 months was not inferior in patients who were treated with NSAIDs (11). In terms of pleurodesis for spontaneous pneumothorax, it has been reported that the use of an NSAID obviates the need for narcotics without increasing the risk of recurrence (12).

The intrapleural administration of local analgesia just before the administration of the sclerosing agent has been suggested (9, 13); however, there is little evidence to support this recommendation. Furthermore, the present study shows that non-administration of lidocaine (1%) did not increase the risk of chest pain. A prospective study is needed to determine whether the administration of lidocaine (1%) has any benefit in patients undergoing pleurodesis. Pleurodesis with minocycline is reported to cause chest pain (14). However, the risk of chest pain was not increased in this study. This is thought to be due to the small number of patients who underwent pleurodesis with minocycline.

The present study is associated with several limitations, including its retrospective nature, single-center design, small study population, and a patient selection bias. In addition, this study did not review the relationship between success or failure of pleurodesis, the complications of pleurodesis and the outcomes. Furthermore, in Japan, OK-432 is the preferred sclerosing agent, whereas in Western countries, talc pleurodesis has been the gold standard for the treatment of malignant pleural effusion for many years. Talc pleurodesis also causes chest pain and fever (15, 16). Further investigations are needed to identify the risk factors for complications caused by pleurodesis.

**Table 3.** Univariate Analysis of Factors Associated with Rescue Medication for Chest Pain after Pleurodesis.

| Factor                        | OR   | 95% CI       | p value |
|-------------------------------|------|--------------|---------|
| Age, years                    |      |              |         |
| <70/≥70                       | 2.60 | 1.11-6.10    | 0.028   |
| Sex                           |      |              |         |
| Male/Female                   | 0.75 | 0.32-1.78    | 0.514   |
| Body height, cm               |      |              |         |
| ≥160/＜160                     | 1.43 | 0.62-3.31    | 0.397   |
| Body weight, kg               |      |              |         |
| ≥55/＜55                       | 0.50 | 0.22-1.16    | 0.105   |
| Body surface area, m²         |      |              |         |
| ≥1.6/＜1.6                     | 0.56 | 0.24-1.32    | 0.183   |
| Disease                       |      |              |         |
| Malignant pleural effusion    | 1.07 | 0.47-2.41    | 0.877   |
| Albumin, g/dL                 |      |              |         |
| ≥3.2/＜3.2                     | 0.77 | 0.34-1.75    | 0.533   |
| C-reactive protein, mg/dL     |      |              |         |
| ≥3.0/＜3.0                     | 0.87 | 0.38-1.97    | 0.736   |
| 24-h drainage volume on the day before pleurodesis, mL | 1.03 | 0.46-2.34 | 0.936 |
| Dose of OK-432                |      |              |         |
| 10 KE/5 KE                    | 1.93 | 0.47-7.97    | 0.365   |
| Administration of minocycline |      |              |         |
| Yes/No                        | 1.09 | 0.31-3.85    | 0.896   |
| Administration of autologous blood | 2.33 | 0.70-7.74 | 0.168 |
| Volume of solution            |      |              |         |
| 100 mL/≤50 mL                 | 0.96 | 0.42-2.17    | 0.919   |
| Administration of lidocaine 1%|      |              |         |
| No/Yes                        | 0.99 | 0.44-2.24    | 0.979   |
| NSAID                         |      |              |         |
| No/Yes                        | 4.22 | 1.64-10.85   | 0.003   |
| Acetaminophen                 |      |              |         |
| No/Yes                        | 0.44 | 0.17-1.17    | 0.099   |
| Opioid                        |      |              |         |
| No/Yes                        | 0.41 | 0.17-1.01    | 0.053   |

**Table 4.** Multivariate Analysis of Factors Associated with Rescue Medication for Chest Pain after Pleurodesis.

| Factor                        | OR   | 95% CI       | p value |
|-------------------------------|------|--------------|---------|
| Age                           |      |              |         |
| <70/≥70                       | 2.97 | 1.10-8.00    | 0.031   |
| Administration of autologous blood | 3.19 | 0.85-12.05  | 0.086   |
| NSAID                         |      |              |         |
| No/Yes                        | 4.21 | 1.47-12.04   | 0.007   |
| Acetaminophen                 |      |              |         |
| No/Yes                        | 0.72 | 0.16-3.18    | 0.662   |
| Opioid                        |      |              |         |
| No/Yes                        | 0.68 | 0.18-2.51    | 0.557   |

OR: odds ratio, CI: confidence interval, NSAID: nonsteroidal anti-inflammatory drug.
Prospective studies are needed to further investigate this issue.

Management of chest pain in adults of <70 years of age. Prophylactic administration of lidocaine 1% to prevent pain caused by pleurodesis with OK-432. Furthermore, caution is advised in the management of chest pain in adults of <70 years of age. It might be better to consider premedication with a non-steroidal anti-inflammatory drug (NSAID) for the need for rescue medication for the management of chest pain. The absence of premedication with an NSAID were risk factors for the need for rescue medication for the management of chest pain. It might be better to consider premedication with an NSAID to prevent the chest pain caused by pleurodesis with OK-432 and talc.

In conclusion, this study showed that age <70 years and administration of minocycline were risk factors for the need for rescue medication for the management of chest pain. It might be better to consider premedication with an NSAID to prevent the chest pain caused by pleurodesis with OK-432 and talc. Furthermore, caution is advised in the management of chest pain in adults of <70 years of age. Prospective studies are needed to further investigate this issue.

The authors state that they have no Conflict of Interest (COI).

**Authorship**

Y. Morimoto performed the study and wrote the paper. H. Takei, K. Tachibana, Y. Nakazato, R. Tanaka, Y. Nagashima, K. Watanabe, R. Seki, T. Shinohara, and H. Kondo contributed to the analysis and interpretation of data, and assisted in the preparation of the manuscript.

**Ethics**

The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee at Kyorin University Hospital (approval number: 776).

**Table 5. Univariate Analysis of Factors Associated with Fever after Pleurodesis.**

| Factor                              | OR  | 95% CI            | p value |
|-------------------------------------|-----|-------------------|---------|
| Age, years                          |     |                   |         |
| <70/≥70                             | 2.07| 0.88-4.84         | 0.095   |
| Sex                                 |     |                   |         |
| Male/Female                         | 1.68| 0.68-4.14         | 0.260   |
| Body height, cm                     |     |                   |         |
| ≥160/＜160                          | 1.67| 0.71-3.91         | 0.240   |
| Body weight, kg                     |     |                   |         |
| ≥55/＜55                            | 0.90| 0.39-2.07         | 0.801   |
| Body surface area                   |     |                   |         |
| ≥1.6/＜1.6                          | 0.84| 0.36-1.95         | 0.681   |
| Disease                             |     |                   |         |
| Malignant pleural effusion          | 1.38| 0.60-3.15         | 0.447   |
| Albumin, g/dL                       |     |                   |         |
| ≥3.2/＜3.2                          | 1.00| 1.04-2.28         | 0.999   |
| C-reactive protein, mg/dL           |     |                   |         |
| ≥53.0/＜3.0                         | 1.65| 0.71-3.80         | 0.242   |
| 24-h drainage volume on the day     |     |                   |         |
| before pleurodesis, mL              |     |                   |         |
| ≥150/＜150                          | 1.15| 0.50-2.63         | 0.740   |
| Dose of OK-432                      |     |                   |         |
| 10KE/5KE                            | 3.00| 0.60-14.99        | 0.181   |
| Administration of minocycline       |     |                   |         |
| Yes/No                              | 0.29| 0.06-1.43         | 0.128   |
| Administration of autologous blood  |     |                   |         |
| Yes/No                              | 0.61| 0.18-2.16         | 0.448   |
| Volume of solution                  |     |                   |         |
| 100 mL/≤50 mL                       | 2.22| 0.95-5.20         | 0.067   |
| Administration of lidocaine 1%      |     |                   |         |
| No/Yes                              | 1.83| 0.80-4.22         | 0.154   |
| NSAID                               |     |                   |         |
| No/Yes                              | 2.67| 1.08-6.60         | 0.034   |
| Acetaminophen                       |     |                   |         |
| No/Yes                              | 0.60| 0.23-1.57         | 0.298   |
| Opioid                              |     |                   |         |
| No/Yes                              | 0.94| 0.39-2.30         | 0.900   |

OR: odds ratio, CI: confidence interval, KE: Klinische Einheit, NSAID: nonsteroidal anti-inflammatory drug

**Table 6. Multivariate Analysis of Factors Associated with Fever after Pleurodesis.**

| Factor                              | OR  | 95% CI            | p value |
|-------------------------------------|-----|-------------------|---------|
| Age                                 |     |                   |         |
| <70/≥70                             | 1.86| 0.75-4.59         | 0.181   |
| Dose of OK-432                      |     |                   |         |
| 10KE/5KE                            | 1.12| 0.16-7.81         | 0.906   |
| Administration of minocycline       |     |                   |         |
| Yes/No                              | 0.37| 0.06-2.48         | 0.305   |
| Volume of solution                  |     |                   |         |
| 100 mL/≤50 mL                       | 2.00| 0.79-5.03         | 0.141   |
| NSAID                               |     |                   |         |
| No/Yes                              | 2.43| 0.95-6.22         | 0.065   |

OR: odds ratio, CI: confidence interval, KE: Klinische Einheit, NSAID: nonsteroidal anti-inflammatory drug

The authors state that they have no Conflict of Interest (COI).

**Authorship**

Y. Morimoto performed the study and wrote the paper. H. Takei, K. Tachibana, Y. Nakazato, R. Tanaka, Y. Nagashima, K. Watanabe, R. Seki, T. Shinohara, and H. Kondo contributed to the analysis and interpretation of data, and assisted in the preparation of the manuscript.

**References**

1. Yoshida K, Sugiu T, Takifuji N, et al. Randomized phase II trial of three intrapleural therapy regimens for the management of malignant pleural effusion in previously untreated non-small cell lung cancer: JCOG 9515. Lung Cancer 58: 362-368, 2007.
2. Kasahara K, Shibata K, Shintani H, et al. Randomized phase II trial of OK-432 in patients with malignant pleural effusion due to non-small cell lung cancer. Anticancer Res 26: 1495-1499, 2006.
3. How CH, Tsai TM, Kuo SW, et al. Chemical pleurodesis for prolonged postoperative air leak in primary spontaneous pneumothorax. J Formos Med Assoc 113: 284-290, 2014.
4. Ishida A, Miyazawa T, Miyazu Y, et al. Intrapleural cisplatin and OK432 therapy for malignant pleural effusion caused by non-small cell lung cancer. Respir Med 11: 90-97, 2006.
hancement of surface expression of ICAM-1 on tumor cells in vivo. Clin Immunol Immunopathol 78: 283-290, 1996.

6. Tsuchiya I, Kasahara T, Yamashita K, et al. Induction of inflammatory cytokines in the pleural effusion of cancer patients after the administration of an immunomodulator, OK-432: role of IL-8 for neutrophil infiltration. Cytokine 5: 595-603, 1993.

7. Fulop T, Larbi A, Douziech N, et al. Signal transduction and functional changes in neutrophils with aging. Aging Cell 3: 217-226, 2004.

8. Linton PJ, Dorschkind K. Age-related changes in lymphocyte development and function. Nat Immunol 5: 133-139, 2004.

9. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ; BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax 65 (Suppl 2): ii32-ii40, 2010.

10. Hunt I, Teh E, Southon R, Treasure T. Using non-steroidal anti-inflammatory drugs (NSAIDs) following pleurodesis. Interact Cardiovasc Thorac Surg 6: 102-104, 2007.

11. Rahman NM, Pepperell J, Rehal S, et al. Effect of opioids vs NSAIDs and larger vs smaller chest tube size on pain control and pleurodesis efficacy among patients with malignant pleural effusion: the TIME1 randomized clinical trial. JAMA 314: 2641-2653, 2015.

12. Ben-Nun A, Golan N, Faibishenko I, Simansky D, Soudack M. Nonsteroidal antiinflammatory medications: efficient and safe treatment following video-assisted pleurodesis for spontaneous pneumothorax. World J Surg 35: 2563-2567, 2011.

13. Kvale PA, Sellecky PA, Prakash UB; American College of Chest Physicians. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 132: 368S-3403S, 2007.

14. Ng CK, Ko FW, Chan JW, et al. Minocycline and talc slurry pleurodesis for patients with secondary spontaneous pneumothorax. Int J Tuberc Lung Dis 14: 1342-1346, 2010.

15. Neragi-Miandoab S. Malignant pleural effusion, current and evolving approaches for its diagnosis and management. Lung Cancer 54: 1-9, 2006.

16. Inoue T, Ishida A, Nakamura M, Nishine H, Mineshita M, Miyazawa T. Talc pleurodesis for the management of malignant pleural effusions in Japan. Intern Med 52: 1173-1176, 2013.