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ORIGINAL ARTICLE

Usefulness of suplatast tosilate for chronic cough following lung cancer surgery

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Abstract
Objective. Chronic dry cough is reported to occur in about 25% of patients following lung cancer surgery. Experimental data suggest that it may be caused mainly by stimulation of C-fibers, which are widely distributed to the lower trachea and bronchi. We assessed the clinical usefulness of suplatast tosilate (IPD) for chronic dry cough after lung cancer surgery.
Methods. The subjects were patients with stage I lung cancer who had undergone lobectomy combined with mediastinal lymph node dissection. IPD was administered orally at 400 mg daily, and its efficacy was evaluated by patient interview 1, 2, and 3 months after the start of treatment. The subjects were 19 patients, and the duration of cough before entering the study was 393.2 days.
Results. The response rate was 84.2% (16/19) 1 month after the start of treatment. It seems that IPD inhibits cough resulting from stimulation of the bifurcated trachea with a high content of C-fibers.
Conclusion. The present study suggested the efficacy of IPD for controlling chronic dry cough after lung cancer surgery.

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Introduction

In the clinical setting, we encounter patients who develop dry cough after lung cancer surgery. This kind of cough is often refractory and may become chronic, thus impairing the quality of life of affected patients. Suplatast tosilate (IPD), an antiallergy drug that inhibits the production of Th2 cytokines, is reported to be effective for cough refractory to currently available antitussives, such as the cough with variant asthma and atopic cough.[1] The present study assessed the usefulness of IPD for treating patients with chronic dry cough following lung cancer surgery.

Patients and methods

A total of 160 patients with stage I lung cancer had undergone lobectomy with mediastinal lymph node dissection during the period from 2002 to 2007 and had no postoperative complications. Among them, 19 patients who complained of persistent dry cough (refractory to antitussives) of unknown etiology on review after discharge were enrolled in this study. None had underlying diseases that could influence the effectiveness of IPD therapy (e.g., asthma, allergic bronchitis), and they all gave informed consent to participate in the study.

IPD was administered orally twice daily (after breakfast and supper) at a dose of 400 mg/day. The treatment period was determined for each patient individually. Patients were interviewed once a month for 3 months to

evaluate the efficacy of this drug, which was classified into three grades: improved, unchanged, or worsened. Administration was discontinued in patients who were rated as unchanged or worsened, and administration was continued for up to 3 months in patients who were improved and agreed to continue treatment. The patients were also followed to assess recurrence of cough after completion of the treatment.

Results

The clinical characteristics of the subjects are shown in Table 1. It was confirmed that these patients did not have any other possible causes of cough (pleurisy, bronchopneumonia, reflux esophagitis, resumption of smoking, or treatment with angiotensin-converting enzyme inhibitors). Only patients who complained of dry cough refractory to existing antitussives, including codeine, were enrolled.

After 1 month of treatment, 16 patients were rated as improved, 3 patients were unchanged, and no patient was worse than before. The efficacy rate was 84.2%. Of the 11 responders who continued treatment, 10 achieved more improvement after 2 months. Among these 10 patients, 9 showed further improvement after 3 months of treatment. Among the 16 responders who completed the scheduled treatment, the aggravated condition was observed in 3 cases after treatment (Fig. 1).

All three patients who were rated as worse after the completion of treatment had received the drug for 3 months, and they subsequently continued to take it. The three patients who were rated as unchanged after 1 month of treatment were all heavy smokers. One was an elderly woman aged 85 years, another was treated with a daily dose of 300 mg (100 mg three times a day), and the third had undergone bilateral mediastinal lymph node dissection via midline sternotomy.

Discussion

Chronic dry cough is reported to occur in about 25% of patients following lung cancer surgery.[2] Experimental findings suggest that it may be largely caused by stimulation (e.g., due to bradykinin, tobacco) of C-fibers, which are widely distributed to the lower trachea and bronchi.[3–5] The theory that C-fibers are involved in the development of chronic cough is based on a report that capsaicin, which selectively stimulates C-fibers, causes cough in humans and other animals.[6–8] C-fibers are

Table 1 Patient characteristics ($n = 19$)

Variable	Result
Age (years), mean ± SD and range	65.8 ± 9.0 (53–85)
Sex	
Male	12
Female	7
Preoperative smoker	
Yes	9
No	10
Preoperative stage	
A	10
B	9
Operative approach	
VATS	4
Standard	14
Median	1
Duration of cough before the study (days)	393.2 ± 146.6
Period of administration (days)	101.5 ± 106.6
Daily dose of administration	
300 mg	3
400 mg	15
600 mg	1

VATS, video-assisted thoracic surgery

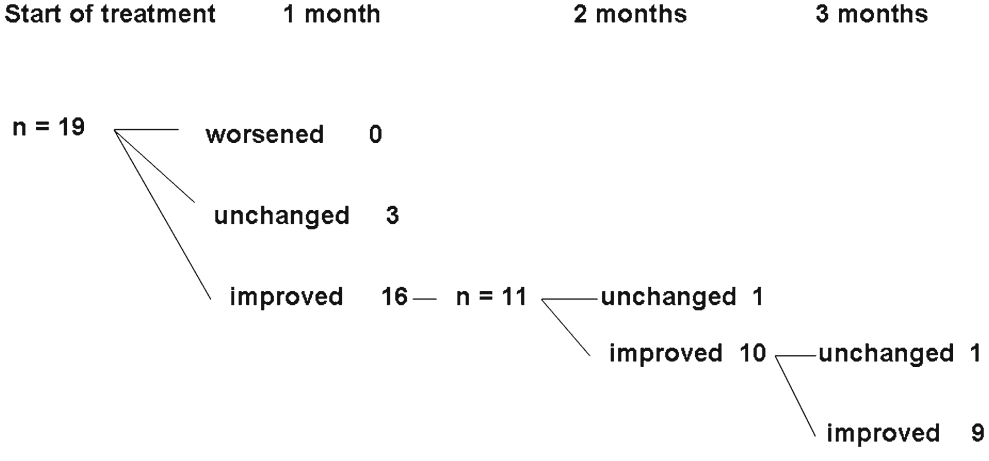

Fig. 1 Effect of IPD on cough. Efficacy was evaluated 1, 2, and 3 months after the start of treatment by patient interview and was classified into three grades: improved, unchanged, worsened

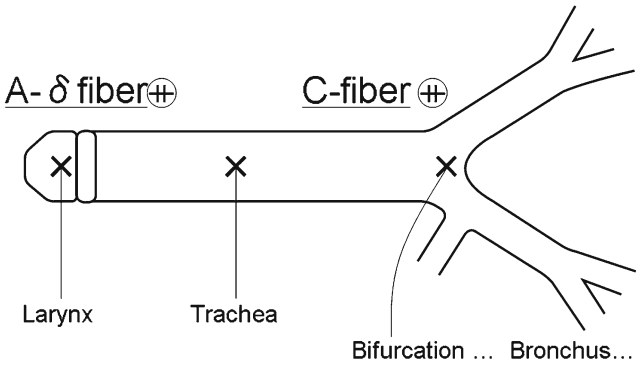

Fig. 2 Distribution of cough-related nerve fibers. C-fibers are widely distributed in the airways and are most common in the peripheral regions, whereas A-δ fibers are mainly distributed in the larynx

widely distributed in the airways and are more common in their peripheral regions, where 70%–80% of the sensory nerves are said to consist of C-fibers. Cough arising from stimulation of the larynx is inhibited by codeine, whereas cough caused by stimulation of the trachea that has a high content in C-fibers is poorly inhibited by narcotics or similar drugs and can be persistent. Therefore, it is presumed that such cough occurs after lung cancer surgery as a result of injury to the bronchi during lobectomy or to the trachea during mediastinal lymph node dissection.[9] (Fig. 2).

An antiallergy drug that inhibits Th2 cytokine production, IPD has been shown to be effective for coughing that is refractory to existing antitussives, including cough variant asthma and atopic cough.[1,10–14] IPD has been shown to inhibit bradykinin-induced discharge of afferent nerves in the lower airways, thereby suppressing persistent cough caused by stimulation of the trachea, to which C-fibers (codeine-resistant nerve fibers involved in the induction of cough) are widely distributed.[15,16]

In the present clinical study, 16 of the 19 patients (84.2%) responded to IPD. To minimize the influence of factors such as differences in the stage of the cancer or the surgical approach, the study targeted patients with stage I lung cancer who had undergone lobectomy and mediastinal lymph node dissection with no postoperative complications. The mean duration of cough before enrollment in this study was 393.2 days. Only three patients did not respond to IPD, and all were heavy smokers. One of them received IPD at a daily dose of 300 mg, which may have been insufficient. Another patient had undergone extended surgery (bilateral mediastinal lymph node dissection via midline sternotomy), so the extensive surgical invasion may explain the failure of treatment. Three patients (18.8%) showed recurrence after discontinuation of treatment, but their symptoms were controlled after resumption of IPD. These results are considered quite satisfactory.

Conclusion

This study provides suggestive evidence that IPD inhibits cough caused by stimulation of the bifurcated trachea, which has a high content in C-fibers. It also presents suggestive clinical evidence indicating that IPD benefits refractory chronic dry cough following lung cancer surgery.

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