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ORIGINAL ARTICLE

Efficacy of nebulized acetylcysteine for relieving symptoms and reducing usage of expectorants in patients with radiation pneumonitis

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Keywords
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Abstract

Background: Radiation pneumonitis is one of the most harmful and clinically significant complications of radiotherapy. This study investigated the benefits of nebulized acetylcysteine for lung cancer patients diagnosed with radiation pneumonitis after radiotherapy.

Methods: We prospectively enrolled and followed 25 patients with radiation pneumonitis who used nebulized acetylcysteine three times a day for 12 weeks. We also reviewed the medical records of 106 control patients who had undergone radiotherapy for lung cancer but had not used acetylcysteine. We evaluated the effects of nebulized acetylcysteine by comparing visits 1 and 4 among nebulizer users and by comparing the acetylcysteine group with the control group.

Results: Twenty-five acetylcysteine group patients and 101 control group patients were included in the analyses. The mean patient-rated severity score associated with sputum production decreased in the acetylcysteine group between visits 1 and 4 (from 1.10 to 0.95; $P = 0.08$). None of the patients used additional expectorant agents after using nebulized acetylcysteine and critical adverse events were not reported. The acetylcysteine group had a shorter mean duration of expectorant use among patients whose radiation pneumonitis required steroid therapy and covered > 10% of a single lung field on computed tomography (37.2 vs. 78.1 days, respectively; $P = 0.07$).

Conclusions: The beneficial effects of nebulized acetylcysteine for patients with radiation pneumonitis included relieving sputum severity and minimizing expectorant use, especially in severe cases. Further investigation is required to clarify and expand on the benefits of nebulized acetylcysteine for patients with radiation pneumonitis.

Introduction

Radiation pneumonitis is one of the most hazardous complications of concurrent chemoradiation for lung cancer and esophageal cancer.[1,2] Since concurrent chemoradiotherapy began to demonstrate benefits for locally advanced lung cancer,[3] radiotherapy has remained an important component of treatment. However, other than supportive care, there is no established treatment for radiation pneumonitis. Although some experimental agents, such as pentoxifylline and amifostine, have been studied,[4,5] it would be challenging to use experimental agents in clinical contexts.

Acetylcysteine, one of longest established and most potent mucolytics,[6] has been used as a nebulized and systemic agent. Nebulized acetylcysteine, a free sulfhydryl reagent that cleaves disulfide bonds within mucus glycoproteins and liquefies sputum, is well known to be effective for reducing sputum viscosity and stimulating expectoration.[7] Radiation contributes to mucosal damage and the

inhibition of mucociliary clearance,[8,9] which hinders expectoration; expectorants may be helpful in relieving the resulting congestion and associated symptoms. Additionally, N-acetylcysteine is known to have potent antioxidant effects by enhancing glutathione production. Because of these effects, other studies have investigated the efficacy of N-acetylcysteine in combating other forms of interstitial pneumonitis, including idiopathic pulmonary fibrosis.[10,11] Therefore, it is reasonable to hypothesize that the antioxidant and mucolytic effects of inhaled acetylcysteine may promote healing and slow down the progression of fibrosis in radiation pneumonitis.

Although the efficacy of ambroxol for radiation pneumonitis has previously been studied[12] – and even though acetylcysteine was originally developed as an inhaled agent – to our knowledge, there are no published reports of well-designed studies that show the benefits of nebulized acetylcysteine.

This study investigated the potential benefits of inhaled acetylcysteine for lung cancer patients with radiation pneumonitis using spirometry and symptom evaluation.

Methods

Patient group information

We prospectively recruited 25 lung cancer patients from Asan Medical Center (Seoul, South Korea) who were diagnosed from 1 May 2015 with radiation pneumonitis based on computed tomography (CT) scans and symptoms. Patients were excluded if: (i) they were aged > 80 years; or if they had (ii) infectious pneumonia, (iii) asthma, (iv) heart failure with pulmonary edema, (v) chronic obstructive pulmonary disease with < 50% of predicted forced expiratory volume after 1 second (FEV_1), or with dyspnea more severe than modified Medical Research Council (MRC) grade 2, because such patients usually use additional bronchodilators and mucolytics, which could act as confounders. Gender, age, weight, height, smoking history, Eastern Cooperative Oncology Group performance status, prior expectorant history, type of lung cancer, and grade of radiation pneumonitis were evaluated on day 1.

This study was approved by the institutional review board of Asan Medical Center, Seoul, South Korea and was performed in accordance with the principles of the Declaration of Helsinki (Number: 2015-1202).

Control group information

Additional control group data were retrospectively collected from the Asan Biomedical Research Environment (ABLE) program. We screened the medical records of 676 lung cancer patients who had undergone radiotherapy between 1 May 2015 and 31 October 2017. Patients were excluded if they had been prescribed nebulized acetylcysteine more than once. Among the 676 patients, radiologists diagnosed 106 patients with radiation pneumonitis by CT. Duration of expectorant use and oral steroid prescription data were collected by reviewing electronic medical records. To compensate for the severity of radiation pneumonitis, we only conducted comparisons between the acetylcysteine and control groups in patients who received steroid therapy for radiation pneumonitis. As a study by Yin *et al.* suggested that the mucociliary system recovers within three months to one year of damage onset and because the antioxidant effect could be diminished after the termination of pathological processes,[13] we excluded patients with an interval between diagnosis of radiation pneumonitis and use of nebulized acetylcysteine of > 1 year. A clinician evaluated the extensiveness of radiation pneumonitis on CT.

Patient group management

Patients in the acetylcysteine group were prescribed 4 mL of nebulized acetylcysteine (Mucomyst solution, Boryung Pharmaceutical Co. Ltd, Seoul, South Korea) three times per day for 12 weeks. For safety, patients were educated about nebulizer use and adverse effects; during the first nebulization session patients were observed for one hour for anaphylaxis and bronchospasm. All patients visited the clinic every four weeks during the 12-week regimen. At every follow-up visit, patients were asked about adverse events, compliance, symptoms, and use of additional expectorants. Symptoms were evaluated using a questionnaire-based scoring system with a scale ranging from 0 to 4: 0, no symptoms; 1, very mild; and 5, very severe. FEV_1 and forced vital capacity (FVC) were measured at visits 1 and 4 using a spirometer.

Subgroup analysis

We conducted subgroup analysis to compensate for differences in the severity of radiation pneumonitis between the acetylcysteine and control groups. Subgroups consisted of patients who were prescribed corticosteroids whose radiation pneumonitis covered > 10% of a single lung field on CT. Patients with a > 1 year interval between diagnosis of radiation pneumonitis and initiation of nebulized acetylcysteine were excluded. Example images of patients whose radiation pneumonitis covered > 10% on CT are shown in Figure 1.

Statistics

Differences in patients' symptoms and spirometry values between visits 1 and 4 were compared using the paired *t*-test. If a patient missed a clinic visit, within-group and between-group comparisons were made using the latest

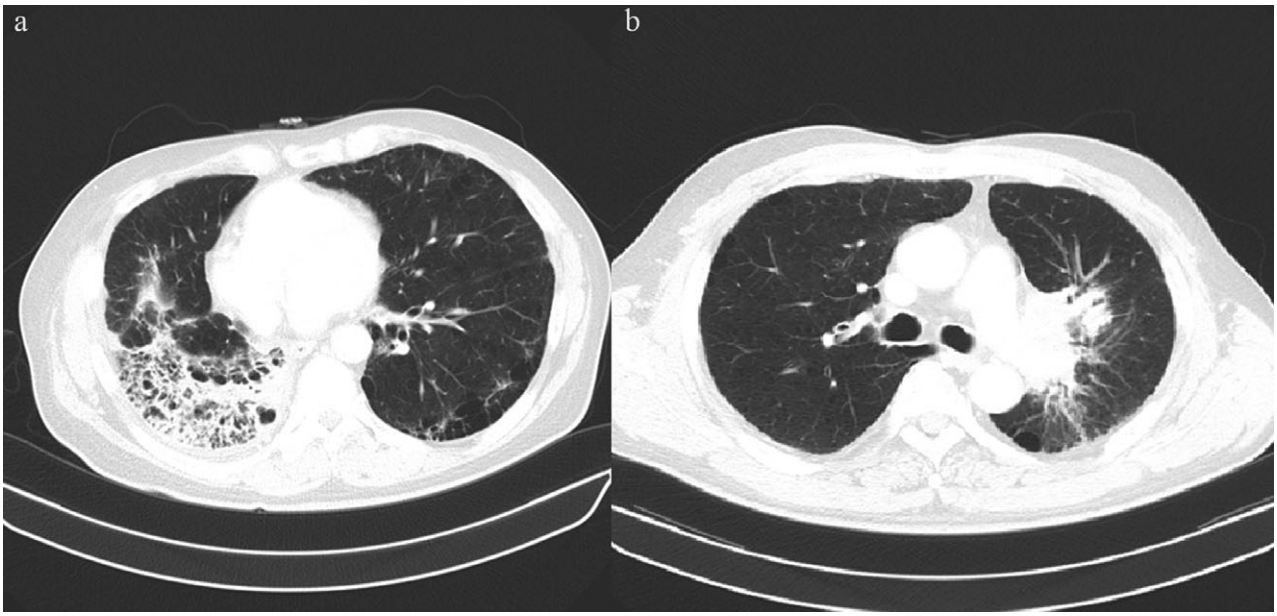

Figure 1 Computed tomography images of patients whose radiation pneumonitis covered > 10%: (**a**) right lung fibrosis and consolidation; (**b**) left lung fibrosis and patchy consolidations with reticular change.

data available. A Student's *t*-test was used to compare the duration of expectorant and steroid use between the groups. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The significance level was set at $P = 0.1$.

Results

Patient group information

There were 20 male and 5 female patients in the acetylcysteine group, at an average age of 62.4 years. Patient characteristics are shown in Table 1. The adverse events experienced were as follows: two patients reported oral pain as a result of oral mucositis, one patient experienced facial edema, one patient experienced nasal obstruction, and one patient reported a headache. There were no serious adverse events, and administration of acetylcysteine was not terminated as a result of adverse events. Four patients were excluded from the analysis because they were lost to follow-up after the first visit.

Table 1 Characteristics of the participants

Characteristics	Acetylcysteine group (n = 25)	Control group (n = 101)
Age	62.4 (34–73)	66.6 (25–85)
Median value	64	68
Male gender	20 (80)	89 (88)
Height	165.5 (149–179)	NA
Weight	70.0 (50–105)	NA
ECOG PS		
1	21 (84)	NA
2	1 (4)	NA
3	1 (4)	NA
Pathology		
Adenocarcinoma	9 (36)	29 (29)
Squamous cell carcinoma	10 (40)	49 (49)
Small cell cancer	2 (8)	19 (19)
Other	2 (8)	2 (2)
FEV_1	1.9 ± 0.6	2.2 ± 0.6
Forced vital capacity	3.1 ± 1.0	3.3 ± 0.7
Radiation pneumonitis grade		
Grade 1	13 (52)	NA
Grade 2	9 (36)	NA
Smoking history	33.4 ± 27.8	NA
Use of steroid	16 (64)	37 (36.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; FEV_1, forced expiratory volume in 1 second.

In-group analyses

The mean cough, dyspnea, and chest discomfort severity scores declined over time; however, the changes were not statistically significant (Fig 2). The mean cough severity score decreased from 1.24 to 1.19 ($P = 0.67$), dyspnea from 1.05 to 1.00 ($P = 0.33$), and chest discomfort from 0.52 to 0.48 ($P = 0.33$). There was also no significant change in FVC (3.41 L to 3.34 L; $P = 0.59$). However, there was a meaningful reduction in the sputum severity (viscosity) score from 1.10 to 0.95 ($P = 0.08$). At visit 1, 16 patients (76.2%) required additional expectorant agents, but none of the patients were using additional expectorants by their last visit.

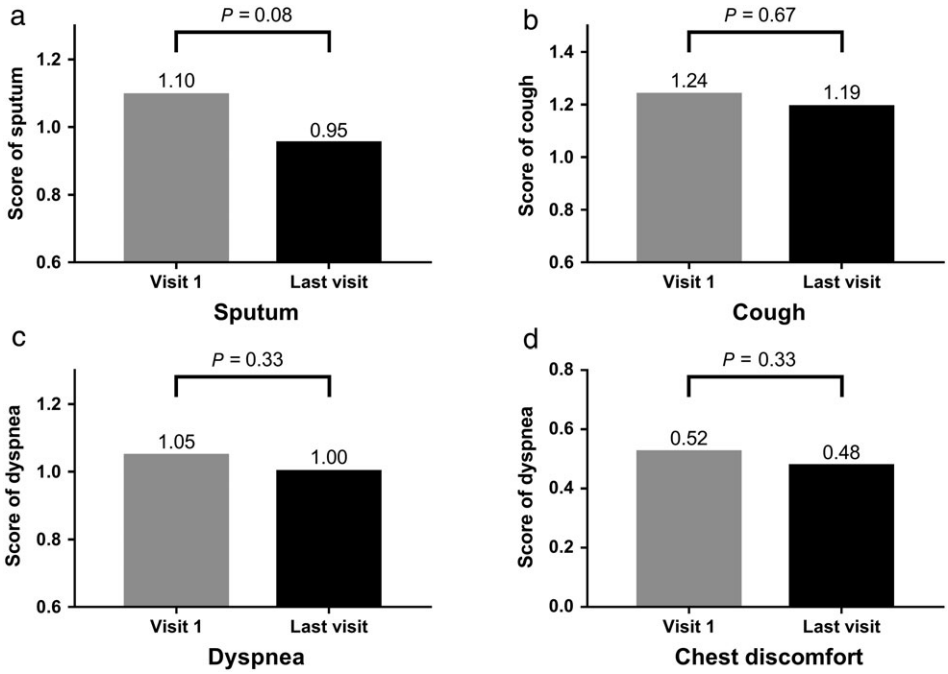

Figure 2 Comparisons in the nebulizer group between the first and last visits: (**a**) sputum, (**b**) cough, (**c**) dyspnea, and (**d**) chest discomfort scores.

Comparison between patient and control groups

Among the 106 control group patients, one was excluded because of Cushing disease, which would have confounded the analysis because of the associated hypoadrenalism, and four patients were excluded because of short follow-up intervals (< 6 months). In the control group, 37 patients were prescribed steroids to treat radiation pneumonitis. The characteristics of patients who received steroid therapy are summarized in Table 2.

There was no significant difference in the duration of steroid and expectorant use between the groups (Fig 3). The mean duration of expectorant use among patients in the acetylcysteine group was 67.8 days, compared to 54.5 days in the control group ($P = 0.54$). The mean duration of steroid use was 57.6 days in the acetylcysteine group, compared to 69.1 days in the control group ($P = 0.42$).

Subgroup analysis

Subgroup analysis comparing patients who received corticosteroids and whose radiation pneumonitis covered over 10% of a single lung field on CT at the time of diagnosis revealed a mean duration of expectorant use in the acetylcysteine group of 37.2 days, which was meaningfully lower than the 78.1 days found in the control group ($P = 0.07$).

Table 2 Characteristics of patients who required steroids

Characteristics	Total (n = 47)	Acetylcysteine group (n = 10)	Control group (n = 37)
Age	67.4 (34–82)	58.9 (34–70)	69.8 (44–82)
Male gender	37 (88)	7 (70)	30 (81)
Pathology			
Adenocarcinoma	18 (38.3)	3 (30)	15 (40.5)
Squamous cell carcinoma	20 (42.6)	4 (40)	16 (43.2)
Small cell cancer	6 (12.8)	1 (10)	5 (13.5)
Other	3 (6.4)	2 (20)	1 (2.7)
Extent on CT > 10%	35 (74.4)	9(90)	26(70.2)

CT, computed tomography.

Discussion

To the best of our knowledge, this is the first study to evaluate the benefits of nebulized acetylcysteine for patients with radiation pneumonitis. This study demonstrated the potential benefits of nebulized acetylcysteine for patients with radiation pneumonitis in terms of relieving symptom severity (particularly sputum viscosity) and helping to reduce the use of expectorants, especially among patients with more severe radiation pneumonitis on CT. Although we did not demonstrate or compare statistical significance, no patients required additional expectorant agents after using nebulized acetylcysteine.

Although amifostine, a potent scavenger of oxygen free radicals, seems to reduce radiation pneumonitis and

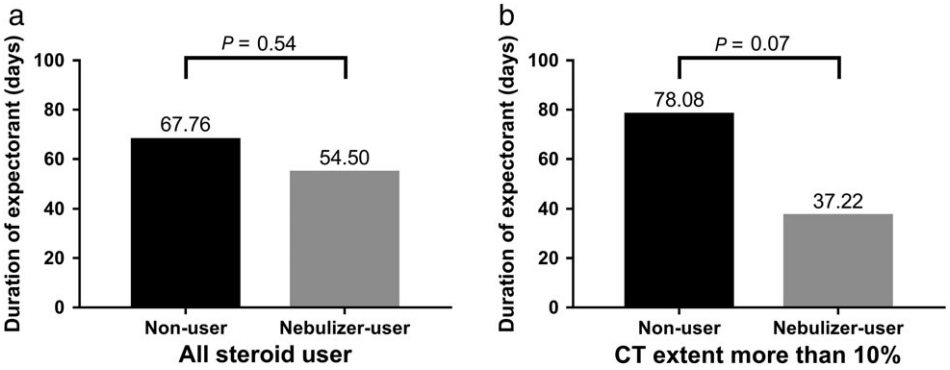

Figure 3 Comparison of duration of expectorant in patients requiring steroids: (**a**) all steroid users; (**b**) patients with computed tomography (CT) extent > 10%.

esophagitis,[5,14,15] it causes many adverse effects, including nausea, vomiting, and cardiovascular toxicity.[16] Pentoxifylline has also been shown to prevent radiation-induced lung damage,[4] but it would be challenging for clinicians to use in real practice. Nebulized acetylcysteine, which has been used for a long time, represents an ideal option for both clinicians and patients if proven efficacious for radiation pneumonitis treatment, especially given the lack of serious adverse events associated with its use in our series.

Our findings are consistent with previous studies. Even without effecting a significant change in cytokine levels (such as of TGF-β1 and TGFα), ambroxol, which is an expectorant also known to reduce free radicals, has been shown to minimize reduction of diffusion capacity, and reduce incidence of radiation pneumonitis.[12] Additionally, Homma *et al.* reported beneficial effects of inhaled acetylcysteine on the stability of FVC and the diffusing capacity of carbon monoxide for patients with early idiopathic pulmonary fibrosis.[11] Acetylcysteine has also been associated with improvement of transplant-free survival among antinuclear-antibody-positive idiopathic pulmonary fibrosis patients.[10] These studies suggest that the antioxidant and expectorant effects of acetylcysteine are efficacious against inflammatory fibrotic conditions of the lung, such as radiation pneumonitis.

Our study had several limitations. As this was a pioneering study of the effect of nebulized acetylcysteine on radiation pneumonitis, it had a small sample size, making statistically significant results difficult to obtain. This small sample size also contributed to difficulties matching the groups according to age and gender. Additionally, this study was not a randomized trial and the control group data were collected via medical record review, thus there might have been differences between the groups, such as the severity and extent of radiation pneumonitis, which were not fully adjusted for in the analysis. We only analyzed patients who required corticosteroid therapy for radiation pneumonitis to compensate for this discrepancy, but other factors contribute to the severity and prognosis of radiation pneumonitis. All patients in the acetylcysteine group had mild symptoms, and this could have led to difficulties finding differences in symptom scores and FVC. Also, we performed subgroup analysis for severe cases by analyzing the patients who required steroid therapy and those who had > 10% of a single lung field affected on CT. The severity criteria were based on the observation that steroid therapy is not normally used in mild asymptomatic patients and the finding that a volume of lung that receives > 20 Gy of ionizing radiation has an increased risk of radiation pneumonitis.[17,18] Therefore, there could be discrepancies in terms of clinical severity. Additional randomized controlled trials with diverse patient characteristics and larger sample sizes are required to definitively demonstrate the benefits of acetylcysteine for patients with radiation pneumonitis.

In conclusion, we found that nebulized acetylcysteine could provide beneficial effects for patients with radiation pneumonitis, particularly to relieve sputum severity and reduce the use of additional expectorant agents, especially in severe cases. Further investigation is required to elaborate and clarify the benefits of nebulized acetylcysteine therapy for radiation pneumonitis.

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Disclosure

No authors report any conflict of interest.

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