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Support

Supported by the National Cancer Center Research and Development Fund (Grants No. 23-A-16, 23-A-18, and 26-A-4) and Grants-in-Aid for Cancer Research (Grants No. 20S-2 and 20S-6) from the Ministry of Health, Labour, and Welfare of Japan.

GLOSSARY TERMS

cisplatin: an inorganic platinum agent (cis-diamminedichloroplatinum) with antineoplastic activity. Cisplatin forms highly reactive, charged, platinum complexes, which bind to nucleophilic groups such as GC-rich sites in DNA, inducing intrastrand and interstrand DNA cross-links as well as DNA-protein cross-links. These cross-links result in apoptosis and cell growth inhibition. Carboplatin and oxaliplatin are other members of this class.

docetaxel: a member of the taxane group of antimitotic chemotherapy medications whose mode of action is to bind and stabilize microtubules and thus disrupt cell division.

non–small-cell lung cancer (NSCLC): a type of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.

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Acknowledgment

Presented at the 47th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 3-7, 2011. We thank the members of the Japan Clinical Oncology Group Data Center and Operations Office for their support in article preparation (Drs Junko Eba and Kenichi Nakamura), data management (Tomoko Kazato), and oversight of the study management (Dr Haruhiko Fukuda). Furthermore, we thank the members of the West Japan Oncology Group Data Center.

Appendix

Reasons for Bolus Cisplatin Administration Unsuitability

Patients age 70 to 74 years were examined before enrollment for the following six conditions, which defined them as unsuitable for bolus cisplatin administration (Appendix Table A1): a combination of more than one mild organ dysfunction, but violating none of the inclusion criteria; a combination of comorbid illness and mild organ dysfunction, but violating none of the inclusion criteria; organ dysfunction not specified by the inclusion/exclusion criteria; a combination of more than one comorbid illness; a comorbid illness not specified by the exclusion criteria; or any other condition.

Procedures of Administration

In the docetaxel monotherapy arm, docetaxel was diluted with 250 to 500 mL of 5% glucose solution or physiologic saline and administered by intravenous infusion over 60 minutes.

In the docetaxel plus cisplatin (DP) arm, docetaxel was diluted with 250 mL of 5% glucose solution or 200 mL of physiologic saline and administered by intravenous infusion over 60 minutes. Cisplatin was administered by intravenous infusion over 15 to 20 minutes, directly or after being diluted with physiologic saline, after docetaxel administration. A total of 1,000 to 1,500 mL of fluid was administered before and after the administration of cisplatin. During treatment with cisplatin, careful attention was paid to urinary output, and diuretics such as mannitol and furosemide were administered if necessary. Antiemetics such as 5-hydroxytryptamine-3 receptor antagonists and steroids were also administered if necessary.

Dose Reduction Criteria and Methods

In both arms, the presence of grade 4 neutropenia, febrile neutropenia, or grade $\geq$ 3 nonhematologic toxicity (except anorexia, nausea, vomiting, hyponatremia, constipation, and hyperglycemia) necessitated dose reduction (docetaxel arm levels -1 and -2: docetaxel 50 and 40 mg/m^2, respectively; DP arm level -1: docetaxel 15 mg/m^2 and cisplatin 20 mg/m^2). In addition, if serum creatinine levels exceeded 2.0 mg/dL, the administration of cisplatin was stopped in subsequent cycles in the DP arm. The persistence of these toxicities after two dose-reduction steps in the docetaxel arm or one dose-reduction step of each drug in the DP arm prompted treatment discontinuation.

Definition of Overall and Progression-Free Survival

Overall survival was measured from the date of random assignment to death from any cause and was censored at the last follow-up date. Progression-free survival was measured from the date of random assignment to the first observation of disease progression or death from any cause if there was no progression. If there was no progression and the patient did not die, progression-free survival data were censored at the date on which the absence of progression was confirmed.

Table A1. Conditions Defining Patients As Unsuitable for Bolus Cisplatin Administration

Condition	No. of Patients	
	Docetaxel (n = 31)	Docetaxel/Cisplatin (n = 32)
Combination of more than one mild organ dysfunction, but violating none of the inclusion criteria	6	4
Combination of comorbid illness and mild organ dysfunction, but violating none of the inclusion criteria	5	8
Organ dysfunction not specified by the inclusion/exclusion criteria	8	3
Combination of more than one comorbid illness	1	7
Comorbid illness not specified by the exclusion criteria	2	2
Any other condition	9	8

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Support Care Cancer (2015) 23:905–912
DOI 10.1007/s00520-014-2430-x

ORIGINAL ARTICLE

Therapeutic and preventive antiemetic effect of aprepitant in Japanese patients with thoracic malignancies who truly need it

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Received: 12 June 2014 / Accepted: 2 September 2014 / Published online: 17 September 2014
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Abstract
Purpose Neurokinin-1 (NK-1) receptor antagonist is recommended for chemotherapy-induced nausea and vomiting (CINV) in highly emetogenic chemotherapy (HEC) and has recently been introduced to oncology practice in Japan. However, whether all patients undergoing HEC truly need NK-1 receptor antagonist remains unknown, and increasing medical costs due to uniform use of NK-1 receptor antagonist are a concern. This study was conducted to examine the prevalence of patients who needed aprepitant at the time of its introduction in Japan, and therapeutic and preventive effects of aprepitant on HEC or moderately emetogenic chemotherapy (MEC).
Patients and methods Eligible patients with thoracic malignancies who were to undergo HEC or MEC received 5-hydroxytryptamine receptor antagonists and dexamethasone to prevent CINV. Aprepitant was administered to treat CINV occurring in the first course, or to prevent CINV in the second course. Frequency of vomiting, degree of nausea, and quality of life with respect to CINV were assessed.
Results In total, 96 patients were enrolled. Aprepitant was not administered in 57 and 88 % of patients who received HEC and MEC, respectively. In patients treated with aprepitant (n=18), therapeutic use of aprepitant after occurrence of CINV (n=9) decreased average scores in numerical rating scale for nausea from 7.44 to 5.44 (p=0.10), and average frequency of vomiting per day from 2.11 to 0.11 (p=0.03). Prophylactic use of aprepitant in the second course (n=18) increased the proportion of patients with no significant nausea from 6 % (first course) to 50 % (second course; p=0.007), and those with no vomiting from 33 to 89 % (p=0.002). Aprepitant use also significantly improved quality of life with respect to CINV in the second course.
Conclusion More than half of patients receiving HEC and 88 % of patients receiving MEC did not use aprepitant. Aprepitant showed significant therapeutic and preventive effects on CINV in patients who truly needed it.

Keywords Aprepitant · Neurokinin-1 receptor antagonist · Chemotherapy-induced nausea and vomiting · Therapeutic effect · Prophylactic effect · Quality of life

Electronic supplementary material The online version of this article (doi:10.1007/s00520-014-2430-x) contains supplementary material, which is available to authorized users.

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse event in patients treated with highly or moderately emetogenic chemotherapy (HEC or MEC). Cisplatin and carboplatin, which are key drugs in the treatment of thoracic cancer, frequently cause nausea and vomiting and

are classified as highly or moderately emetogenic agents. Nausea and vomiting not only reduce the quality of life of patients but also cause difficulty in oral ingestion, a serious problem that affects the continuation of treatment.

Vomiting is caused by stimulation of the vomiting center in the medulla oblongata. There are several pathways of vomiting stimulus conduction to the vomiting center: the path through chemoreceptor trigger zone in the fourth ventricle, afferent vagal nerve pathways from the gastrointestinal tract, and cerebral cortex induced by memories or impressions [1–3]. Neurokinin-1 (NK-1) receptor is highly expressed in the nucleus of the solitary tract, part of the vomiting center in the brainstem, and vomiting is induced by substance P binding to the receptor [2]. Aprepitant, an NK-1 receptor antagonist that became available in Japan in 2010, has been shown to have a preventive effect for nausea and vomiting induced by HEC. Aprepitant is also effective against delayed emesis, which is often difficult to control by conventional antiemetic treatment [4–6], and is recommended in guidelines for CINV in many countries [7–9]. The antiemetic guidelines classify anticancer agents by their emetogenicity into four categories—high, moderate, low, and the minimum emetogenic risk—and a three-drug preventive antiemetic combination comprising NK-1 receptor antagonist, 5-hydroxytriptamine (5-HT_3) receptor antagonist, and corticosteroid has been recommended for HEC and, if appropriate, for MEC. However, it is well known that CINV is controllable by conventional two-drug preventive antiemetic therapy that does not include NK-1 receptor antagonists in 40 to 70 % of patients treated by HEC [10–14]. In clinical practice, nausea and vomiting tend to be experienced the day after administration of anticancer agents with conventional preventive two-drug antiemetic therapy rather than on the day of administration. It has been reported that the release of substance P by anticancer agents increases on day 2 or later following chemotherapy [15, 16]; therefore, NK-1 receptor antagonist might be also effective on day 2 or later. While numerous reports have described prophylactic antiemetic effects of NK-1 receptor antagonists [8–12], to the best of our knowledge, a therapeutic effect of aprepitant after the occurrence of CINV has not been reported. Although the uniform prophylactic use of aprepitant is recommended in guidelines regardless of demographic risk factors, increased medical costs owing to uniform use of NK-1 receptor antagonists are a concern. When the current antiemetic guidelines were released following the approval of aprepitant in Japan, questions and concerns regarding how and whether the uniform prophylactic administration of aprepitant was truly needed were raised in the oncology clinic in Aichi Medical University Hospital. These questions prompted us to conduct this study to reveal the proportion of patients who truly need aprepitant, and to elucidate its therapeutic and preventive effect in patients who truly needed it.

Methods

This single institutional non-randomized prospective study was conducted after approval from the Institutional Review Board for Aichi Medical University School of Medicine.

Patients

Patients, aged 20 years or older, able to use the Japanese language, and receiving HEC or MEC for thoracic malignancies in the Division of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine, and who had given written informed consent before the onset of chemotherapy, were eligible.

Study design

All patients received standard antiemetic therapy consisting of intravenous granisetron and dexamethasone to prevent CINV. The prophylactic antiemetic regimen for HEC consisted of granisetron 1 mg intravenous (iv) and dexamethasone sodium phosphate 20 mg iv on day 1 before chemotherapy, and dexamethasone sodium phosphate 20 mg iv on days 2–3. The prophylactic antiemetic regimen for MEC consisted of granisetron 1 mg iv and dexamethasone sodium phosphate 12 mg iv on day 1 before chemotherapy, and dexamethasone sodium phosphate 8 mg iv on days 2–3. A patient who needed aprepitant was defined as a patient who experienced CINV and received aprepitant for therapeutic intent and/or received aprepitant for prophylactic intent in the subsequent courses of chemotherapy. Aprepitant was administered to patients who needed it to treat CINV in the first course when CINV occurred, or to prevent CINV in the second course. Aprepitant dose started at 125 mg on day 1, followed by 80 mg once a day orally, for a total of 3 days. All patients who experienced CINV in the first course received prophylactic aprepitant for the second course. Use of other antiemetic agents for rescue therapy was not limited.

Assessment

Patients completed the demographic questionnaire at onset of chemotherapy and kept a diary to monitor the antiemetic efficacy from day 1 to day 7. The diary documented vomiting episodes, use of rescue therapy, and daily nausea rating on a numerical rating scale (NRS): 0 indicated no nausea and 10 recorded nausea that was "as bad as it could be" [17]. They also completed the Functional Living Index-Emesis (FLIE) questionnaire Japanese version on day 6 [18]. Two pharmacists trained specifically for this study visited each patient on days 1 and 6 and, according to need, assisted them in the proper completion of the patient diary, reminded them to take

the study medication as directed, and reminded them to complete the FLIE questionnaire.

Efficacy was recorded form the initiation of chemotherapy infusion (0 h) to day 7 on chemotherapy. At post-initiation of chemotherapy, 0–24 and 24–144 h were defined as "acute" and "delayed" time frames, respectively, while 0–144 h was defined as the "overall" time frame. Patients who did not receive second course of chemotherapy were excluded from the efficacy analysis.

Efficacy of antiemetic therapy was evaluated as follows: (1) "no vomiting," no vomiting or retching; (2) "no rescue," no use of other antiemetics including dopamine D_2 receptor antagonist, histamine H_2 receptor blocker, proton pump inhibitor, histamine H_1 receptor blocker, and drip infusions to cover a reduced oral intake; (3) "no nausea," nausea of NRS=0; (4) "no significant nausea," nausea of NRS≤2; (5) "complete response," no vomiting and no use of rescue therapy during the overall time frame; and (6) "complete protection," no vomiting with no rescue therapy and nausea of NRS≤2.

Quality of life was assessed using the patient-reported FLIE questionnaire Japanese version. The FLIE questionnaire is a validated instrument for measurement of the impact of CINV on daily living, consisting of a nausea domain (nine items) and a vomiting domain (nine items) [18]. The questionnaire was administered on day 6, which is within the overall time frame. Responses to each question were rated on a 100-mm visual analog scale that was scored on a 1- to 7-point scale. For most items, the larger the score, the worse the effect on the patients' quality of life; the reverse was true for some items, for which the scores were reversed so that all items had the same direction.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Costs incurred for antiemetic medicines used during this study were estimated from clinical record data using the drug price for 2011. Antiemetic medicines included aprepitant, 5-HT_3 receptor antagonists, corticosteroids, and rescue medicines including dopamine D_2 receptor antagonists, histamine H_2 receptor blockers, proton pump inhibitors, histamine H_1 receptor blockers, and drip infusions to cover a reduced oral intake. All costs were converted from Japanese yen to US dollars based on Organization for Economic Co-operation and Development (OECD) purchasing power parity in 2013 ($1=¥100).

Statistical analysis

The primary objective of this study was to elucidate the prevalence of patients who needed aprepitant. The secondary objectives were therapeutic effects of aprepitant when it was administered after CINV occurred in the middle of the course, preventive effects of aprepitant on CINV when it was administered at the onset of the second course of HEC or MEC, and its impact on quality of life with respect to CINV. At least 65 patients were needed to ensure a 95 % confidence interval of ±20 % around the estimated prevalence of patients who needed aprepitant with a power of 0.8. The preventive effects of aprepitant for emesis were assessed in the overall phase (days 1–5), acute phase (day 1), and delayed phase (days 2–5). Wilcoxon signed-ranks test or paired t test was performed at a two-sided significance level of 0.05 to compare the therapeutic and prophylactic efficacy before and after administration of aprepitant and to compare the FLIE scores between patients who did and did not receive aprepitant. The Fisher's exact test was used to compare proportions of patients with the following: (1) no vomiting, (2) no rescue, (3) no nausea, (4) no significant nausea, (5) complete response, and (6) complete protection.

The prevalence of vomiting, nausea, and aprepitant usage for each factor of demographic background was evaluated using the Fisher's exact test. Univariate analyses were then performed to identify relationships between each factor of demographic background and the ratio of vomiting, nausea and aprepitant usage. Potential correlations between aprepitant usage and those demographic factors that had $p<0.15$ in the univariate analysis were evaluated using multivariate logistic regression. Results were defined as significant if p was <0.05, and 95 % confidence intervals (95 % CIs) were calculated.

Results

From June 2011 to January 2013, 96 patients were enrolled in the study, 77 of whom were assessable. Nineteen patients were excluded from the efficacy analysis because they did not receive the second course of chemotherapy because of adverse events ($n=12$), received aprepitant prophylactically from the first course ($n=1$), or failed to provide efficacy data ($n=6$). Patient characteristics are listed in Table 1. Twenty-eight patients received HEC containing cisplatin and 49 received MEC containing carboplatin, irinotecan, or amrubicine. Nine patients received aprepitant after CINV occurred in the first course and received it prophylactically in the second course; another 9 patients received aprepitant prophylactically at the onset of the second course and 59 patients did not receive aprepitant. Of patients who received HEC, 43 % used aprepitant, and only 12 % of patients who received MEC used aprepitant.

In nine patients who received aprepitant after CINV occurred in the first course of chemotherapy, the average frequency of vomiting reduced from 2.11 to 0.11 times/day ($p=0.03$). However, reduction of average NRS score for nausea was not significant (Fig. 1). The patient characteristics of

Table 1 Patient characteristics

	No. of patients	(%)
Age, years		
Median	67	
Range	38–85	
Gender		
Male	64	(83.1)
Female	13	(16.9)
Histology		
Lung	72	(93.5)
Adenocarcinoma	31	(40.3)
Squamous cell carcinoma	12	(15.6)
Large cell carcinoma	1	(1.3)
Non-small cell carcinoma	3	(3.9)
Small cell carcinoma	19	(24.7)
Others	6	(7.8)
Thymoma/thymic carcinoma	3	(3.9)
Cancer of unknown primary	2	(2.6)
Emetogenicity of chemotherapy		
High	28	(36.4)
Cisplatin doublet	21	(27.3)
Cisplatin doublet+bevacizumab	3	(3.9)
Cisplatin doublet+concurrent radiotherapy	4	(5.2)
Moderate	49	(63.6)
Carboplatin doublet	27	(35.1)
Carboplatin doublet+bevacizumab	4	(5.2)
Carboplatin doublet+concurrent radiotherapy	7	(9.1)
Single agent	11	(14.3)

those who needed aprepitant and those who needed no aprepitant did not differ significantly, except for the emetogenicity of chemotherapy used (HEC or MEC, Supplementary Table S1). Similarly, the patient characteristics of those who needed therapeutic aprepitant and those who did not need aprepitant at all or needed prophylactic-only aprepitant did not differ significantly, except for the emetogenicity of chemotherapy (Supplementary Table S2). These results support our observation of the therapeutic antiemetic effect of aprepitant after chemotherapy-induced vomiting occurred.

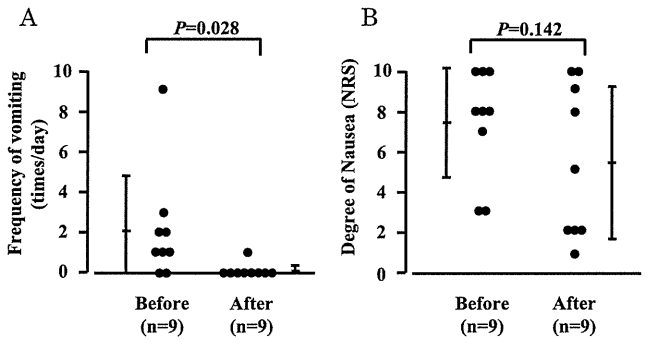

Fig. 1 Therapeutic effect of aprepitant added to the conventional antiemetic regimen consisting of 5-hydroxytriptamine (5-HT_3) receptor antagonists and dexamethasone on chemotherapy-induced vomiting (**a**) and nausea (**b**)

In patients who needed aprepitant, the prevalence of no vomiting, no rescue, no significant nausea, and complete response increased significantly in the delayed time frame in the second course, although the increment did not reach statistical significance in the acute time frame (Table 2). Average frequency of vomiting and average degree of nausea significantly reduced in the second course, except for frequency of vomiting in MEC (Table 3).

In patients who received HEC and needed aprepitant, the prevalence of no vomiting and no rescue significantly increased in the delayed time frame of second course (Table 2). In patients who received MEC and needed aprepitant, the prevalence of no rescue and no significant nausea in delayed time frame also significantly increased (Table 2).

The impact on daily living was assessed using the FLIE questionnaire. In patients who did not need aprepitant, the prevalence of patients with no impact on daily living (NIDL) was generally high and did not change during two courses of chemotherapy. In contrast, in patients who needed aprepitant, the prevalence of NIDL was low in the first course and significantly improved in the second course (Table 4).

Univariate analysis to assess the relationships between each demographic factor and vomiting, nausea and aprepitant usage, benzodiazepine usage, information from acquaintances regarding CINV, alcohol consumption, and defecation, the amount eaten at the last meal before chemotherapy and emesis risk of chemotherapy were extracted as risk factors of emesis. Incidence of vomiting was lower in patients who consumed less than half of their last meal before chemotherapy with marginal significance (p=0.05). Nausea occurred more frequently in patients who received HEC than those who received MEC (79 vs 49 %, p=0.02). Fewer patients who defecated every day used aprepitant compared with patients who did not (16 vs 45 %, p=0.01).

In multivariate analysis using a multiple logistic regression model, benzodiazepine use, information from acquaintances regarding CINV, and alcohol habit were used as variables. HEC was significantly correlated with nausea (odds ratio [OR] 4.38, 95 % CI 1.26–15.17, p=0.02) and aprepitant use (OR 5.47, 95 % CI 1.42–21.14, p=0.01), but insignificantly with vomiting (OR 2.21, 95 % CI 0.61–7.98, p=0.23). Benzodiazepine use was inversely correlated with aprepitant use (OR 0.16, 95 % CI 0.03–0.91, p=0.04).

Medical costs for antiemetic treatment during two courses of chemotherapy were evaluated. The mean costs of antiemetic treatment for patients who did not use aprepitant in the first and second courses were $7.6 and $8.7, respectively. For

Table 2 Efficacy end points

		No aprepitant needed (n=59)					Aprepitant needed (n=18)				
		Acute[b]		Delayed			Acute[b]		Delayed		
		1st course	2nd course	1st course	2nd course	p value[a]	1st course	2nd course	1st course	2nd course	p value[a]
Total	No vomiting (%)	100	100	88.1	91.5	0.762	77.8	100	44.4	88.9	0.012
	No rescue (%)	98.3	94.9	62.7	55.9	0.568	100	88.9	0	50.0	0.001
	No nausea (%)	89.8	88.1	59.3	57.6	1.000	44.4	50.0	0	11.0	0.486
	No significant nausea (%)	100	98.3	81.4	78.0	0.820	61.1	77.8	5.6	44.4	0.018
	Complete response (%)	100	98.3	78.0	76.3	1.000	55.6	77.8	5.6	38.9	0.041
	Complete protection (%)	98.3	93.2	57.6	50.8	0.580	55.6	50.0	0	16.7	0.229
HEC	No vomiting (%)	100	100	87.5	93.8	1.000	75.0	100	50.0	100	0.014
	No rescue (%)	100	93.8	56.3	43.8	0.724	100	83.3	0	41.7	0.037
	No nausea (%)	87.5	87.5	43.8	43.8	1.000	16.7	41.7	0	8.3	1.000
	No significant nausea (%)	100	100	62.5	68.8	1.000	41.7	83.3	16.7	33.3	0.640
	Complete response (%)	100	100	75.0	68.8	1.000	41.7	83.3	8.3	33.3	0.317
	Complete protection (%)	100	93.8	56.3	37.5	0.479	41.7	50.0	0	8.3	1.000
MEC	No vomiting (%)	100	100	88.4	90.7	1.000	83.3	100	33.3	66.7	0.567
	No rescue (%)	97.7	95.3	67.4	65.1	1.000	100	100	0	66.7	0.061
	No nausea (%)	90.7	88.4	65.1	62.8	1.000	100	66.7	0	16.7	1.000
	No significant nausea (%)	100	71.2	61.0	59.3	1.000	100	66.7	0	66.7	0.061
	Complete response (%)	100	97.7	79.1	79.1	1.000	83.3	66.7	0	50.0	0.182
	Complete protection (%)	97.7	93.0	58.1	55.8	1.000	83.3	50.0	0	33.3	0.455

No nausea = nausea score 0; no significant nausea = nausea score 0, 1, 2 by NRS; complete response = no vomiting and no significant nausea; complete protection = no vomiting, no significant nausea, and no rescue therapy

HEC highly emetogenic chemotherapy, *MEC* moderately emetogenic chemotherapy

[a] Result of statistical analysis by Fisher's exact test compared with incidence of each item in the first course and second course of delayed phase were shown in p value columns

[b] There was no statistical significance in incidence in all of items in acute phase

patients who needed aprepitant after CINV occurred in the first course and prophylactically in the second course, the average total cost of medicines for antiemetic treatment was $156.9 in the first course and $165.8 in the second course. In patients

Table 3 Prophylactic effect of aprepitant on chemotherapy-induced nausea and vomiting

	No aprepitant needed (n=59)			Aprepitant needed (n=18)		
	1st course	2nd course	p value	1st course	2nd course	p value
Total (n=77)						
Frequency of vomiting	0.20±0.64	0.15±0.61	0.594	1.50±2.12	0.11±0.32	0.014
Degree of nausea	1.37±1.91	2.33±0.61	0.789	6.94±2.94	3.00±2.85	0.027
HEC (n=28)						
Frequency of vomiting	0.25±0.77	0.06±0.25	0.383	1.75±2.49	0.00±0.00	0.010
Degree of nausea	1.94±2.21	2.00±2.37	0.864	6.58±3.03	3.17±2.48	0.033
MEC (n=49)						
Frequency of vomiting	0.19±0.59	0.19±0.70	1.000	1.00±1.10	0.33±0.52	0.175
Degree of nausea	1.16±1.77	1.23±2.31	0.829	7.50±2.88	2.67±3.72	0.024

Frequency of vomiting (times/day) and degree of nausea measured by NRS were extracted from emesis diary patients recorded, and the worst point was used for calculating average. Statistical analysis was performed by pared t test (mean ± SD)

HEC highly emetogenic chemotherapy, *MEC* moderately emetogenic chemotherapy

Table 4 Patients with "no impact on daily life" by chemotherapy-induced nausea and vomiting

	No aprepitant needed (n=59)			Aprepitant needed (n=18)		
	1st course	2nd course	p value	1st course	2nd course	p value
Total (%)	83.1	84.7	>0.999	16.7	55.6	0.035
Frequency of vomiting (%)	91.5	94.9	0.717	44.4	94.4	0.003
Degree of nausea (%)	74.6	76.3	>0.999	11.1	44.4	0.060

"No impact on daily life" by CINV was defined as an FLIE score of no less than 2 in each item. Statistical analysis was performed by Fisher's exact test

who received prophylactic aprepitant only in the second course, the mean total cost of medicines for antiemetic treatment increased from $21.7 in the first course to $115.5 in the second course (Fig. 2).

Discussion

Antiemetic guidelines recommend a combination of three antiemetics including NK-1 receptor antagonist to prevent CINV induced by HEC [7–9]. However, it has been reported that approximately half of patients who received HEC and a conventional antiemetic regimen without NK-1 receptor antagonists did not experience CINV. Our study has revealed that more than half of patients who received HEC and nine tenths of patients who received MEC did not need aprepitant and that in patients who truly needed aprepitant, it exerted remarkable therapeutic and preventive effect against CINV. This is the first report to elucidate the therapeutic effect of aprepitant on CINV; aprepitant was effective not only for prevention but also for treatment of CINV.

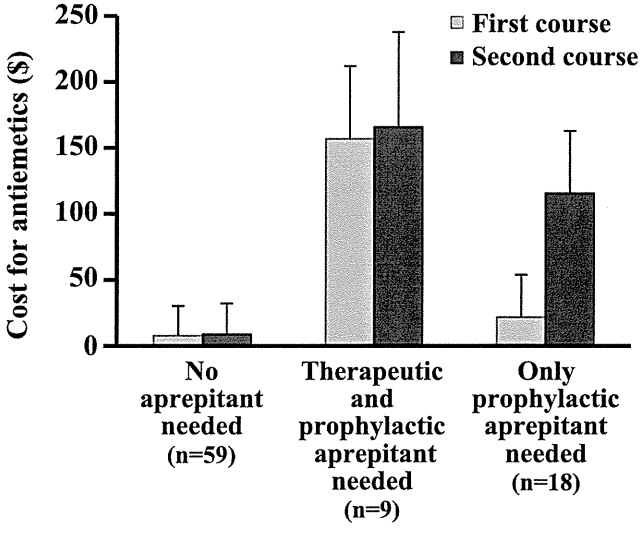

Fig. 2 Total medical cost of antiemetic therapy in patients who needed no aprepitant, both therapeutic and prophylactic aprepitant, or only prophylactic aprepitant. Medical costs included dopamine D_2 receptor antagonists, histamine H_2 receptor blockers, proton-pump inhibitors, histamine H_1 receptor blockers, laxative agents, and drip infusions to cover a reduced oral intake

In more than half of patients who received HEC and approximately 90 % of patients who received MEC, CINV was fairly well controlled without aprepitant. Two thirds of patients who received aprepitant after CINV occurred experienced disappearance of vomiting and reduction of nausea regardless of the type of chemotherapy, HEC or MEC. Frequency of vomiting and the worst degree of nausea reduced by prophylactic administration of aprepitant in the second course. Total FLIE scores also reduced with prophylactic administration of aprepitant in the second course, indicating improved quality of life. These results suggest that aprepitant is highly effective for patients who truly need it.

Antiemetic guidelines recommend aprepitant use from the first course for patients receiving HEC because of the concern that anticipatory emesis before the second course might be induced by a negative experience of CINV in the first course. In this study, however, no patients experienced nausea and vomiting before starting chemotherapy, suggesting that anticipatory emesis did not influence the study results. Vomiting of delayed phase remained in 11.1 % of aprepitant-needed patients, and it was thought to be mostly breakthrough emesis. It has been reported that younger age, female sex, experience of morning sickness during pregnancy, and a previous experience of CINV are risk factors of emesis, while regular alcohol intake inversely correlates with CINV [19–28]. The influence of patients' demographic background on CINV is not clearly understood, and a demographic-background-based antiemetic strategy is not recommended in the CINV guidelines. Here, we identified benzodiazepine use as the only significant negative demographic factor for aprepitant use. Although younger age, female sex, experience of morning sickness during pregnancy, and a previous experience of CINV have been reported as risk factors, we failed to show a significant correlation of these factors with CINV, indicating that we are unable to identify patients who need aprepitant before starting emetogenic chemotherapy.

In this study, we did not limit the use of additional medications that might have antiemetic effects, such as dopamine D_2 receptor antagonists, histamine H_2 receptor blockers, proton pump inhibitors, histamine H_1 receptor blockers, laxative

agents, and drip infusions to cover a reduced oral intake. These additional antiemetics were not administered at the same time with aprepitant to discriminate their antiemetic effect from that of aprepitant. While these medications might be related to the apparently low complete response rate, it also probably assisted aprepitant in reducing CINV. Regarding the therapeutic effects of aprepitant, the following limitations of this study should also be noted. First, it is difficult to demonstrate the therapeutic effect of aprepitant during the same course of the chemotherapy because a placebo effect cannot be excluded. In order to truly prove the therapeutic effect of aprepitant, a placebo-controlled randomized trial (aprepitant vs placebo) is needed. Second, we did not limit the use of additional medications with aprepitant, and we cannot completely exclude their effects. Third, chemotherapy-induced emesis naturally gradually reduces as time goes on, and the improvement of CINV as a result of natural time course cannot clearly be distinguished from therapeutic effects of aprepitant.

Economic concerns regarding the uniform use of aprepitant might reduce aprepitant prescription, leading to low compliance with antiemetic guidelines. Daniel et al. reported a compliance rate of only 10 % with aprepitant, unlike the compliance rates of 60–90 % seen with 5-HT_3 receptor antagonists and dexamethasone [29]. Cost-effectiveness of aprepitant is an issue under debate. Lordick et al. and Annemans et al. reported that aprepitant-based strategy is more effective and less expensive compared with standard care [30, 31]. However, Moore et al. reported that aprepitant provides only modest benefit and would be cost-effective only when the likelihood of delayed CINV or the cost of rescue medications is high [32]. We calculated the total drug cost for antiemetic therapy in the first two courses of chemotherapy. The significant difference in total cost of antiemetics between patients who did and did not need aprepitant was due to the cost of aprepitant and rescue medications. Patients who did not experience CINV on conventional two-drug antiemetics did not need further medical expense with CINV treatment, and their quality of life was not influenced by CINV. On the other hand, patients who needed aprepitant required further antiemetic therapy, and their quality of life was considerably disturbed by CINV. As we have shown in this study, aprepitant is highly effective against CINV especially for those who truly need it. However, considering that we have no effective screening methods to identify those patients before chemotherapy, we agree to follow the current antiemetic guidelines recommending uniform use of aprepitant, at least when prescribing HEC chemotherapy. The results from our study warrant further research to discriminate, before chemotherapy, patients who need extensive antiemetic treatment against CINV and those who do not.

Acknowledgments We thank Mr. Yoshihiro Yamamoto for help in preparing the diary for CINV and Ms. Kanako Tejima for her excellent technical assistance.

Conflict of interest The authors have no conflicts of interest to declare.

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Endoscopic ultrasound-guided fine needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration: Are two better than one in mediastinal staging of non–small cell lung cancer?

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Objective: The role of combined endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) with a single bronchoscope is poorly understood. The purpose of the present study was to elucidate the roles of EBUS-TBNA and EUS-FNA with a single bronchoscope in the preoperative hilar and mediastinal staging of non–small cell lung cancer (NSCLC).

Methods: A total of 150 patients with potentially resectable known or suspected NSCLC were enrolled in our prospective study. EBUS-TBNA was performed, followed by EUS-FNA, with an EBUS bronchoscope for N2 and N3 nodes ≥5 mm in the shortest diameter on ultrasound images, in a single session.

Results: EBUS-TBNA was performed for 257 lymph nodes and EUS-FNA for 176 lymph nodes. Of the 150 patients, 146 had a final diagnosis of NSCLC. Of these 146 patients, 33 (23%) had N2 and/or N3 nodal metastases. The sensitivity of EBUS-TBNA, EUS-FNA, and the combined approach per patient was 52%, 45%, and 73%, respectively (EBUS-TBNA vs the combined approach, $P = .016$, McNemar's test). The corresponding negative predictive value was 88%, 86%, and 93%. Two patients (1%) developed severe cough from EBUS-TBNA.

Conclusions: The combined endoscopic approach with EBUS-TBNA and EUS-FNA is a safe and accurate method for preoperative hilar and mediastinal staging of NSCLC, with better results than with each technique by itself. (J Thorac Cardiovasc Surg 2014;148:1169-77)

GTS

Supplemental material is available online.

Endoscopic ultrasound (EUS)-guided needle techniques, including endobronchial ultrasound-guided (EBUS) transbronchial needle aspiration (EBUS-TBNA) and EUS-guided fine needle aspiration (EUS-FNA), have been recommended as the test of choice for mediastinal staging of non–small cell lung cancer (NSCLC).[1] Although either EBUS-TBNA[2,3] or EUS-FNA[4,5] alone has been found to be an effective method, the combination of EBUS-TBNA and EUS-FNA has been reported to be more accurate than either method alone,[6-10] because EBUS-TBNA and EUS-FNA have complementary roles for mediastinal exploration.[11] However, the combination method has had some issues regarding the availability of expensive equipment and expertise. To overcome these problems, the utility of EUS-FNA with an EBUS bronchoscope in place of an EUS endoscope has been advocated.[12-14] Although the procedure requires some experience and skill, it can be performed by a bronchoscopist with an EBUS bronchoscope and thus enable a simple combined transbronchial and transesophageal endoscopic approach. To date, a few investigators[12,13] have suggested the efficacy of combined EBUS-TBNA and EUS-FNA with an EBUS bronchoscope in the mediastinal staging of NSCLC. However, because no prospective study has clearly demonstrated that the diagnostic value of the combined method is superior to that of each method alone, the roles remain unknown. The purpose of the present study was to elucidate the role of combined EBUS-TBNA and EUS-FNA with a single bronchoscope in preoperative hilar and mediastinal staging of NSCLC. The primary endpoint of the present study was to compare the diagnostic value of the combined method to that of each method by itself. The secondary endpoints were safety and the procedure duration.

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Jan 7, 2014; revisions received April 29, 2014; accepted for publication May 6, 2014; available ahead of print June 13, 2014.

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0022-5223/$36.00

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http://dx.doi.org/10.1016/j.jtcvs.2014.05.023

Abbreviations and Acronyms

CT = computed tomography
EBUS = endobronchial ultrasound
EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration
EUS = endoscopic ultrasound
EUS-FNA = endoscopic ultrasound-guided fine needle aspiration
NSCLC = non–small cell lung cancer
TBNA = transbronchial needle aspiration

METHODS

Patients

We performed a prospective study that had been approved by the institutional review board of Nagoya Medical Center (identifier, 2009-251) and registered with the University Hospital Medical Information Network-Clinical Trials Registry (identifier, UMIN000002882). From December 2009 to August 2012, 150 patients with potentially operable, pathologically proven or clinical or radiologically suspected, NSCLC were enrolled in the present study. The operability was decided from the radiologic findings, including chest computed tomography (CT), positron emission tomography-CT, and brain magnetic resonance imaging, and the patients' condition. Patients with stage T4 or M1 disease according to the International Association for the Study of Lung Cancer staging system[15,16] were excluded. Patients with bulky N2 or N3 disease were also excluded. In our institution, we usually perform bronchoscopy for diagnosis and mediastinal staging in a separate setting; however, we sometimes perform EBUS-TBNA for highly suspicious mediastinal lymph nodes as an initial diagnostic test. Such patients with pathologically proven N2 or N3 disease were not included in the present study. All patients provided written informed consent. The baseline characteristics of the 150 patients are listed in Table 1.

TABLE 1. Patient and lesion characteristics

Characteristic	Value
Patients (n)	150
Gender	
Male	103 (69)
Female	47 (31)
Age (y)	
Mean ± standard deviation	68.3 ± 8.6
Range	33-83
Smoking history	
Never	30 (20)
Former	52 (35)
Current	68 (45)
Primary lesion location by bronchopulmonary segment	
Right upper lobe	51 (34)
Right middle lobe	3 (2)
Right lower lobe	24 (16)
Left upper lobe	34 (23)
Lingula	7 (5)
Left lower lobe	31 (21)
Final histopathologic classification	
Non–small cell lung cancer	
Adenocarcinoma	89 (59)
Squamous cell carcinoma	48 (32)
Large cell carcinoma	3 (2)
Adenocarcinoma + squamous cell carcinoma	2 (1)
Adenocarcinoma + large cell carcinoma	1 (1)
Squamous cell carcinoma + small cell carcinoma	1 (1)
Adenocarcinoma + small cell carcinoma	1 (1)
Sarcomatoid carcinoma	1 (1)
Other	
Small cell carcinoma	2 (1)
Tuberculosis	1 (1)
Organizing pneumonia	1 (1)
Preprocedural diagnosis for non–small cell lung cancer	
Diagnosed	137 (91)
Undiagnosed, but suspected	13 (9)

Data presented as n (%), unless otherwise noted.

Procedures

For EBUS-TBNA and EUS-FNA, a convex probe ultrasound bronchoscope (BF-UC260F-OL8 or BF-UC260FW; Olympus, Tokyo, Japan) and 22-gauge needles (NA-201SX-4022; Olympus) were used. The endoscopic procedures were performed with the patient under local anesthesia with lidocaine and conscious sedation with intravenous midazolam by staff pulmonologists or supervised pulmonary residents. EBUS-TBNA was performed first, followed by EUS-FNA, in a single session.

EBUS-TBNA was performed in the manner similar to the one we have previously described.[17] The procedure was performed with the patient in the supine position. After anesthetizing the upper airway with lidocaine, an EBUS bronchoscope was inserted into the trachea through the mouth, and lidocaine was administered into the trachea and bronchus through the working channel. Next, a balloon attached to the transducer was inflated with saline solution. It was then brought into contact with the airway wall and moved in all directions to identify the lesions for sampling. Once the target lesion had been visualized by ultrasound, a dedicated needle was passed through the working channel of the EBUS bronchoscope and advanced through the tracheobronchial wall into the lesion under real-time ultrasound visualization. After the central stylet had been removed, suction was applied using a syringe while manipulating the needle back and forth within the lesion. After sampling, the suction was released slowly, and the needle was retracted. The specimen collected in the lumen of the needle was first pushed out with the central stylet and then blown by air with a syringe onto a glass slide. The visible tissue fragment on the glass slide was then collected and transferred into numbered separate containers filled with formalin for histologic examination. The remaining specimen on the glass slide was smeared with another glass slide and fixed in 95% alcohol for cytologic examination. To clarify the role and diagnostic ability of each needle aspiration procedure, rapid on-site cytologic examination was not used. EBUS-TBNA was performed for N3 nodes, followed by the N2 nodes that were ≥5 mm in the shortest diameter on the ultrasound images. N1 nodes were examined after the N2 nodes if the attending physician or examiner considered it necessary. Two punctures were made for each lymph node, as previously reported by Herth and colleagues.[18] The lymph node location examined and the duration of the procedure from insertion to removal of an EBUS bronchoscope were recorded.

After EBUS-TBNA, EUS-FNA was performed at the left lateral position, as previously described.[19] An EBUS bronchoscope was inserted and advanced through the esophagus while examining the structure around the esophagus by ultrasound. Once the target lesion had been identified, it was punctured through the esophagus with another needle to avoid contamination from the EBUS-TBNA samples under real-time ultrasound guidance. Next, the needle was manipulated back and forth within the lesion

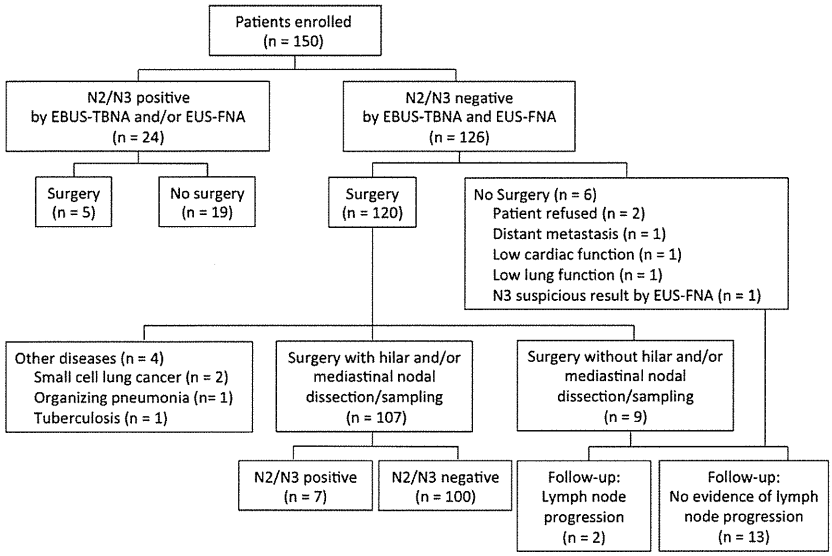

FIGURE 1. Clinical course of patients enrolled in the study. *EBUS-TBNA*, Endobronchial ultrasound-guided transbronchial needle aspiration; *EUS-FNA*, endoscopic ultrasound with bronchoscope-guided fine needle aspiration.

while applying suction under ultrasound guidance and then retracted to collect the aspirated specimen. The handling of the sampled specimens, the size criteria and order in each lymph node for needle aspiration, and the puncture number was the same as for the EBUS-TBNA procedure. To clarify the role and diagnostic ability of each procedure, EUS-FNA was performed even for lymph nodes that had been evaluated using EBUS-TBNA.

Surgical resection with lymph node dissection and/or examination was performed for patients with no evidence of N2 or N3 metastasis and for patients whose attending physician considered it appropriate. An experienced thoracic surgeon decided the operative procedure.

Final Diagnosis

The final diagnosis of lymph node metastases was established by the results of the surgical procedure, EBUS-TBNA and/or EUS-FNA, or radiologic evidence of lymph node progression. If no lymph node progression was seen on CT ≥6 months after EBUS-TBNA and/or EUS-FNA, the lymph nodes were regarded as benign.[20] Suspicious findings from the needle aspiration procedure were regarded as negative in our analysis. The positive findings from the needle aspiration procedure were regarded as true-positive results in our analysis, because the occurrence of false-positive results has been reported to be extremely rare.[1]

TABLE 2. Locations of lymph nodes evaluated by EBUS-TBNA and EUS-FNA

Lymph node location	EBUS-TBNA (n)	EUS-FNA (n)
2R	12	0
2L	0	4
3p	1	3
4R	65	1
4L	56	66
5	0	2
7	77	79
8	0	5
10L	10	16†
11R	20*	0
11L	16	0
Total	257	176

EBUS-TBNA, Endobronchial ultrasound-guided transbronchial needle aspiration; *EUS-FNA*, endoscopic ultrasound-guided fine needle aspiration. *Included 2 N1 lymph nodes. †Included 3 N1 lymph nodes.

Statistical Analysis

The sensitivity of EBUS-TBNA, EUS-FNA, and combined EBUS-TBNA and EUS-FNA approach had been assumed to be 70%, 70%, and 93%, respectively, according to the findings from a previous study.[8] From this information, we planned to accrue ≥129 patients with malignancy to help us detect any superiority in the diagnostic sensitivity of the combined EBUS-TBNA and EUS-FNA procedure compared with a single procedure (EBUS-TBNA or EUS-FNA) at a significance level of 0.05, with 80% statistical power. The homogeneity in the performance of the 2 diagnostic procedures was assessed using the exact McNemar test. Diagnostic sensitivity and the negative predictive value were calculated using the standard definitions, and the 95% confidence intervals were calculated based on the binomial distribution. The mean values and percentages are presented, as appropriate. Continuous variables were analyzed using the Mann-Whitney *U* test. The *P* value was 2-tailed. Statistical analyses were performed using a statistical software program (PASW Statistics, version 18; SPSS, Inc, Chicago, Ill).

RESULTS

Patients

Figure 1 and Figure E1 show the clinical course of the 150 patients enrolled in the present study. A total of 146 patients had a final diagnosis of NSCLC. Of these 146 patients, 121, including 5 with N2- and/or N3-positive results by EBUS-TBNA and/or EUS-FNA, underwent surgery. The surgical procedures were pneumonectomy with nodal dissection or sampling in 3, lobectomy with or without nodal dissection or sampling in 102, segmentectomy with or without nodal dissection or sampling in 6,

TABLE 3. Diagnostic values of EBUS-TBNA and EUS-FNA stratified by patient

	EBUS-TBNA		EUS-FNA		EBUS-TBNA + EUS-FNA	
Diagnostic value	n/Total (%)	95% CI	n/Total (%)	95% CI	n/Total (%)	95% CI
Sensitivity*	17/33 (52)	34-69	15/33 (45)	28-64	24/33 (73)	54-87
Specificity	113/113 (100)	97-100	113/113 (100)	97-100	113/113 (100)	97-100
Positive predictive value	17/17 (100)	81-100	15/15 (100)	78-100	24/24 (100)	85-100
Negative predictive value	113/129 (88)	81-93	113/131 (86)	79-92	113/122 (93)	86-97
Accuracy	130/146 (89)	83-94	128/146 (88)	81-93	137/146 (94)	89-97

EBUS-TBNA, Endobronchial ultrasound-guided transbronchial needle aspiration; *EUS-FNA*, endoscopic ultrasound-guided fine needle aspiration; *CI*, confidence interval. *EBUS-TBNA versus combined approach, $P = .016$; EUS-FNA versus combined approach, $P = .004$; McNemar's test.

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wedge resection with nodal dissection or sampling in 8, and thoracotomy with mediastinal exploration in 2.

EBUS-TBNA and EUS-FNA

Two patients (1%) in whom severe cough had developed during the EBUS-TBNA procedure could not undergo additional EBUS or EUS evaluation. No other complications, including hemorrhage, mediastinitis, or pneumothorax, were observed. The median dose of midazolam used was 4 mg (range, 2-8). EBUS-TBNA was performed for 257 lymph nodes (median, 8.2 mm in the shortest diameter on CT; range, 3.4-17.1) in 121 patients. EUS-FNA was performed for 176 lymph nodes (median, 7.8 mm; range, 4.1-17) in 107 patients. The lymph node locations sampled by the procedures are listed in Table 2.

In the 146 patients with NSCLC, 33 (23%) were diagnosed with N2 or N3 disease. The final tumor and nodal stage and TNM classification determined from the final staging procedures (surgery, endoscopic needle aspiration, or radiologic findings) were as follows: T1 in 71, T2 in 55, T3 in 19, and T4 in 1; N0 in 103, N1 in 10, N2 in 30, and N3 in 3; stage IA in 57, IB in 26, IIA in 16, IIB in 10, IIIA in 29, IIIB in 4, and IV in 4.

The diagnostic values of the procedures per patient are summarized in Table 3. The diagnostic sensitivity of the combined approach was significantly greater than that of each procedure alone (EBUS-TBNA vs combined approach; $P = .016$, EUS-FNA vs combined approach; $P = .004$). The details of the patients with mediastinal metastases diagnosed only by EUS-FNA and EBUS-TBNA are listed in Tables 4 and 5, respectively. Representative patients diagnosed with mediastinal metastasis only by EUS-FNA are shown in Figures 2 and 3. Surgery alone revealed mediastinal metastases in an additional 7 patients (only micrometastases in 2). The lymph node locations were as follows: stations 2R in 1, 4R and 7 in 1, 7 in 1, 5 in 3, and 6 in 1. The positive yield of EBUS-TBNA and EUS-FNA according to lymph node size is presented in Table 6. The sensitivity of EBUS-TBNA and EUS-FNA stratified by lesion is provided in Table 7.

Of the 24 patients with N2 or N3 disease confirmed by EBUS-TBNA and/or EUS-FNA, 19 did not undergo surgical resection but received chemotherapy (n = 7) or chemoradiotherapy (n = 12). The remaining 5 patients underwent surgical resection, followed by chemotherapy (n = 3) or chemoradiotherapy (n = 2).

The duration of the procedures is listed in Table 8. When we examined $\leq$2 lymph nodes, the duration of EUS-FNA was significantly shorter than that of EBUS-TBNA.

DISCUSSION

In the present study, we investigated the efficacy of combined EBUS-TBNA and EUS-FNA with a single bronchoscope in preoperative hilar and mediastinal staging of NSCLC. We demonstrated greater sensitivity with the combined approach than with either alone. In addition, the feasibility and safety were high. We were able to

TABLE 4. Details of 7 patients with mediastinal metastases diagnosed by EUS-FNA but not EBUS-TBNA

Pt. no.	Age (y)	Gender	Histopathologic type	Lymph node location with positive EUS-FNA results (shortest diameter on CT, mm)	EBUS-TBNA
1	76	Male	Squamous cell carcinoma	5 (8.7), 7 (7.5)	Not performed
2	64	Male	Squamous cell carcinoma	5 (16.5)	Not performed
3	65	Female	Squamous cell carcinoma	7 (17.0)	Negative
4	72	Male	Squamous cell carcinoma	7 (9.6)	Negative
5	60	Male	Squamous cell carcinoma	2L (9.5)	Not performed
6	79	Male	Squamous cell carcinoma	4L (7.4)	Negative
7	34	Female	Adenocarcinoma	7 (7.8)	Negative

EUS-FNA, Endoscopic ultrasound-guided fine needle aspiration; *EBUS-TBNA*, endobronchial ultrasound-guided transbronchial needle aspiration; *Pt. no.*, patient number; *CT*, computed tomography.

TABLE 5. Details of 9 patients with mediastinal metastases diagnosed by EBUS-TBNA but not EUS-FNA

Pt. no.	Age (y)	Gender	Histopathologic type	Lymph node location with positive EBUS-TBNA results (shortest diameter on CT, mm)	EUS-FNA
1	70	Male	Adenocarcinoma	4R (12.9)	Not performed
2	54	Male	Non–small cell carcinoma	4R (10.3), 7 (9.5)	Not performed for 4R, suspicious result for 7
3	66	Male	Non–small cell carcinoma	4R (10.3)	Not performed
4	69	Female	Adenocarcinoma	4R (14.2)	Not performed
5	61	Male	Adenocarcinoma	4R (9.9)	Not performed
6	70	Male	Adenocarcinoma	4R (6.0)	Not performed
7	69	Female	Adenocarcinoma	4R (6.0)	Not performed
8	63	Male	Squamous cell carcinoma	4R (10.9)	Not performed
9	76	Male	Squamous cell carcinoma	4R (13.8), 2R (9.7)	Not performed

EBUS-TBNA, Endobronchial ultrasound-guided transbronchial needle aspiration; *EUS-FNA*, endoscopic ultrasound-guided fine needle aspiration; *Pt. no.*, patient number; *CT*, computed tomography.

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complete the procedures in all but 2 patients, who had developed a bad cough during EBUS-TBNA.

The development of EUS endoscopes and EBUS bronchoscopes has dramatically changed the approach to mediastinal staging of NSCLC. Although controversial,[21] several investigators have reported that the diagnostic sensitivity of EBUS-TBNA[3,4] or EUS-FNA[4,5] was similar or greater than that of mediastinoscopy, which has been considered the reference standard for mediastinal staging of lung cancer. Thus, EBUS-TBNA or EUS-FNA has become increasingly accepted as a staging procedure before surgical biopsy.[1,22] A recent review study reported that the diagnostic sensitivity of EBUS-TBNA and EUS-FNA was 89% (range, 46%-97%) and 89% (range, 45%-100%), respectively.[1] Either procedure alone seems sufficiently sensitive as a single method; however, the sensitivity is likely to be affected by the prevalence of the malignancy or suspected nodal locations accessible by each method.[1] Thus, EBUS-TBNA, which can access the paratracheal, subcarinal, and hilar regions, and EUS-FNA, which can access the subcarinal, aortopulmonary window, and lower mediastinal regions, are complementary in the mediastinal staging of lung cancer.[11] EBUS-TBNA and EUS-FNA combined can access nearly all mediastinal lymph nodes. Several investigators[6-10,23] have reported the usefulness of combined EBUS-TBNA and EUS-FNA. Wallace and colleagues[8] compared the diagnostic accuracy of conventional TBNA, EBUS-TBNA, and EUS-FNA for mediastinal staging of lung cancer. These procedures were performed sequentially at the same session in 138 patients.[8] The sensitivity of conventional TBNA, EBUS-TBNA alone, EUS-FNA alone, and combined EBUS-TBNA and EUS-FNA was 36%, 69%, 69%, and 93%, respectively.[8] Szlubowski and colleagues[9] investigated the diagnostic value of EBUS-TBNA and EUS-FNA in 120 patients with NSCLC with normal-size mediastinal nodes. The sensitivity of EBUS-TBNA, EUS-FNA, and combined EBUS-TBNA and EUS-FNA was 46%, 50%, and 68%, respectively (EBUS-TBNA alone vs combined EBUS-TBNA and EUS-FNA, $P = .04$). Annema and colleagues[23] conducted a randomized trial of 241 patients to compare surgical staging alone and combined EBUS-TBNA and EUS-FNA followed by surgical staging. The sensitivity of combined EBUS-TBNA and EUS-FNA followed by surgical staging was significantly greater than surgical staging alone (94% vs 79%, $P = .02$). As these positive

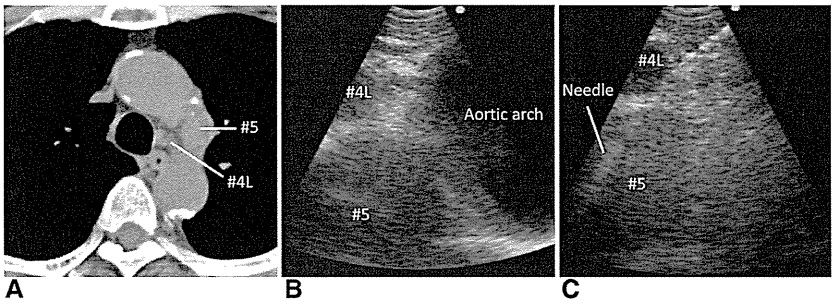

FIGURE 2. Transesophageal endoscopic ultrasound-guided fine needle aspiration for the subaortic lymph node (no. 5), which provided the only evidence of N2 disease (squamous cell carcinoma). The results of endobronchial ultrasound-guided transbronchial needle aspiration and transesophageal endoscopic ultrasound-guided fine needle aspiration for the left lower paratracheal lymph node (no. 4L) were both negative. A, Computed tomography image. B and C, Transesophageal endoscopic ultrasound images.

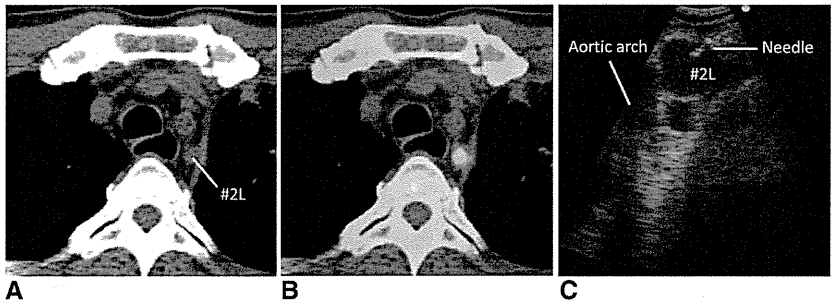

FIGURE 3. Transesophageal endoscopic ultrasound-guided fine needle aspiration for the left upper paratracheal lymph node (no. 2L), which provided the only diagnosis of N2 disease (squamous cell carcinoma). A, Computed tomography image. B, Positron emission tomography-computed tomography image. C, Transesophageal endoscopic ultrasound image.

results have emerged, the combined approach with EBUS-TBNA and EUS-FNA has been described as the best mediastinal staging procedure by endoscopy in recent review studies.[22,24]

Although the accuracy seems to be optimal, the combined EBUS-TBNA and EUS-FNA approach has a serious drawback: the necessity for both an EBUS bronchoscope and an EUS endoscope. Furthermore, most bronchoscopists might not be familiar with the handling of an EUS scope, adding the requirement for an additional experienced endoscopist to perform the combined procedure. The equipment and expertise would not be available in most institutions. In the technique described by Ohnishi and colleagues,[10] each procedure can be performed separately at different specialized centers; however, that could lead to high costs and be time-consuming. To date, several investigators have demonstrated the feasibility, safety, and effectiveness of EUS-FNA with an EBUS bronchoscope for diagnosing benign[19,25] and malignant[12-14,26-28] disease. In the combined transbronchial and transesophageal approach, the use of the EBUS bronchoscope in place of the EUS endoscope for the transesophageal approach is more practical, because all procedures can be performed by a bronchoscopist using an EBUS bronchoscope. The combined approach using a single bronchoscope seems much simpler, more cost effective,[29] and less-time consuming than the approach using both an EBUS bronchoscope and an EUS endoscope. To date, a few studies have reported on its usefulness for preoperative mediastinal staging of lung cancer. Hwangbo and colleagues[13] reported the effectiveness of adding EUS-FNA with an EBUS bronchoscope to EBUS-TBNA in the mediastinal staging of NSCLC. In 150 patients with potentially operable lung cancer, EBUS-TBNA was performed, followed by EUS-FNA for the patients in whom the mediastinal lymph nodes were inaccessible or difficult to access using EBUS. The sensitivity, negative predictive value, and accuracy increased from 84% to 91%, 93% to 96% and 95% to 97% by adding EUS-FNA to EBUS-TBNA, respectively. No complication associated with EUS-FNA was observed in their study.[13] Herth and colleagues[12] investigated the feasibility and efficacy of EBUS-TBNA and EUS-FNA with a single bronchoscope for 150 patients with proven or suspected lung cancer with enlarged mediastinal lymph nodes. They also demonstrated that the combination of EBUS-TBNA and EUS-FNA increased the diagnostic sensitivity compared with each method alone (EBUS-TBNA, 92%; EUS-FNA, 89%; combined approach, 96%) without any complications. Although the sensitivity of the combined approach was greater than that of EBUS-TBNA alone in the studies by Hwangbo and colleagues[13] and Herth and colleagues,[12] the effect of adding EUS-FNA did not seem as large because of the high sensitivity of EBUS-TBNA alone. Our study has shown more clearly the greater effectiveness of adding EUS-FNA to EBUS-TBNA compared with previous studies.

The sensitivity of EBUS-TBNA and EUS-FNA in our study seemed to be lower than that in previous studies. The reasons might have been the low prevalence of

TABLE 6. Yield of EBUS-TBNA and EUS-FNA stratified by mediastinal nodal size on CT

Mediastinal lymph nodes in shortest diameter on CT (mm)	Patients (n)	Total with N2-N3 disease (n)	Patients with positive results (n)		
			EBUS-TBNA	EUS-FNA	EBUS-TBNA + EUS-FNA
<10	107	12	3 (25)	4 (33)	7 (58)
≥10	39	21	14 (67)	11 (52)	17 (81)
Total	146	33	17 (52)	15 (45)	24 (73)

Data in parentheses are percentages. *EBUS-TBNA*, Endobronchial ultrasound-guided transbronchial needle aspiration; *EUS-FNA*, endoscopic ultrasound-guided fine needle aspiration; *CT*, computed tomography.

TABLE 7. Sensitivity of EBUS-TBNA and EUS-FNA per lesion

Lymph node location	Total pathologically proven malignant lesions by surgery or needle aspiration (n)	Positive results (n)*		
		EBUS-TBNA	EUS-FNA	EBUS-TBNA + EUS-FNA
2R	5	4 (80)	0 (0)	4 (80)
2L	1	0 (0)	1 (100)	1 (100)
4R	13	12 (92)	0 (0)	12 (92)
4L	4	1 (25)	4 (100)	4 (100)
5	5	0 (0)	2 (40)	2 (40)
6	1	0 (0)	0 (0)	0 (0)
7	14	7 (50)	10 (71)	12 (86)
Total	43	24 (56)	17 (40)	35 (81)

Data in parentheses are percentages. *EBUS-TBNA*, Endobronchial ultrasound-guided transbronchial needle aspiration; *EUS-FNA*, endoscopic ultrasound-guided fine needle aspiration. *Results of lesions without punctures during EBUS or EUS were regarded as negative.

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malignancy (23%), which has been reported to affect the sensitivity.[1] In addition, our study included consecutive patients with or without enlarged mediastinal lymph nodes, regardless of the lymph node location. In fact, 4 of 7 patients, who had been diagnosed with N2 or N3 disease only by surgery, had single station 5 or 6 lymph node metastases. Other possible reasons include procedural or technical issues, such as the number of aspirations (2 aspirations per lesion in our study) or the level of the examiner's skill. Previous studies of EBUS-TBNA for mediastinal staging of NSCLC have recommended $\geq$2 needle aspirations per lymph node station[30] and >2 lymph node stations.[31] However, optimal results were obtained by 3 needle aspirations[30] and 4 lymph node stations[31] in those studies.

EUS endoscopes have some distinct diagnostic advantages over EBUS bronchoscopes, including the availability of larger and longer needles, better visibility with the endoscope and ultrasound, with a wider ultrasound scanning range, and adjustability of the protruding needle angle using the elevator. These factors are why conventional EUS-FNA surpasses EUS-FNA with an EBUS bronchoscope in diagnostic ability. Although a few studies,[13,26] ours among them, have included a few cases with successful EUS-FNA for the station 5 lymph node, it cannot be assessed by EUS-FNA using an EBUS bronchoscope in most cases. The accessibility of conventional EUS-FNA for station 5 lymph nodes would be much better than that of EUS-FNA with an EBUS bronchoscope. In addition, the adrenal glands[32] or even station 6 lymph nodes[33] can be potentially evaluated using conventional EUS-FNA. Although conventional EUS-FNA was not performed for any patients in our study, it might provide additional diagnostic information in certain cases. Nevertheless, the simplicity of EUS-FNA with an EBUS bronchoscope seems much more practical. One nonrandomized study that included 214 patients with lung cancer suggested that combined EBUS-TBNA and EUS-FNA with a single bronchoscope was equally effective and less time-consuming than combined EBUS-TBNA and conventional EUS-FNA.[14] To resolve the issue regarding whether EUS-FNA with an EBUS bronchoscope can be substituted for that with an EUS endoscope, additional randomized studies are required.

The reason for adding EUS-FNA to EBUS-TBNA is to provide results for the lymph node stations that cannot be assessed using EBUS-TBNA. EUS-FNA can access station 8 or 9 or, occasionally, 5 lymph nodes, which are usually inaccessible using EBUS-TBNA. In addition, it could also

TABLE 8. Duration of procedures stratified by the number of lymph node stations sampled

Lymph node stations sampled (n)	EBUS			EUS			EBUS + EUS*			
		Procedure time (min)			Procedure time (min)			Procedure time (min)		
	Patients (n)	Median	Range	Patients (n)	Median	Range	Patient (n)	Median	Range	*P* value†
0‡	29 (19)	6.5	4.0-23.0	41 (28)	3.5	1.3-14.0	23 (15)	14.8	7.5-34.5	<.01
1	40 (27)	13.9	9.0-36.5	47 (32)	8.8	4.3-21.0	37 (25)	22.5	12.8-39.5	<.01
2	43 (29)	18.8	12.0-43.8	52 (35)	12.5	8.3-28.0	31 (21)	30.8	19.3-56.8	<.01
3	26 (17)	20.8	14.8-41.0	7 (5)	17	15.0-23.0	35 (23)	34	21.8-63.8	.09
4	9 (6)	32.3	23.0-42.0	1 (1)	24	24.0	20 (13)	40.9	35.8-66.3	NA
5	1 (1)	36.8	36.8	0 (0)	—	—	1 (1)	44.3	44.3	NA
6	2 (1)	32	29.5-34.5	0 (0)	—	—	3 (2)	50.3	51-64.8	NA
Total	150 (100)	16.5	4.0-43.8	148 (100)	10.1	1.3-28.0	150 (100)	29	7.5-66.3	<.01

EBUS, Endobronchial ultrasound; *EUS*, endoscopic ultrasound; *NA*, not available. *Duration from EBUS bronchoscope insertion into the trachea until removal from the esophagus. †EBUS versus EUS. ‡Examined by ultrasonography but not sampled because no target lesions were >5 mm.

play an important role for some cases with other lymph nodes difficult to access using EBUS-TBNA, including station 2L, 4L,[13,27] and 7 lymph nodes.[6] The accessibility to station 4L will be much better with EUS-FNA than with EBUS-TBNA in most cases. Even in station 7 lymph nodes, which have been reported as the most frequent location for EBUS-TBNA, the visibility of EUS has been superior to that of EBUS in some cases. Thus, additional EUS-FNA can be recommended, especially for patients with mediastinal lymph nodes that are inaccessible, difficult to access, or not clearly visualized from the airway.

To date, several investigators have suggested that EBUS-TBNA, which provides high sensitivity, can be an alternative to mediastinoscopy.[3,34] Although our study was not designed to compare combined EBUS-TBNA and EUS-FNA with mediastinoscopy, the combined procedure seems to be reasonable as a first pathologic mediastinal staging test, because it can reduce the need for additional invasive surgical staging procedures. However, a substantial number of patients (n = 9) had false-negative EBUS-TBNA and EUS-FNA results in our study; thus, its role seems to be complementary, rather than an alternative, to surgical staging procedures.

A sequential EBUS and EUS examination in a single session seemed to be a well-tolerated and safe procedure. We could complete both procedures in all but 2 patients, who had developed a severe cough during EBUS-TBNA. No other complications were observed except for the minor usual ones associated with endoscopy, such as a minimal amount of blood from the puncture site, a mild cough, or pharyngeal discomfort at EBUS bronchoscope insertion. The present study was performed in the outpatient setting; thus, some minor self-healing complications that occurred after the procedures, including a low-grade fever, might have been underestimated. However, no patients required a specific treatment, including antibiotics for prophylaxis or treatment, in our study.

This was a single-center, nonrandomized study, which was a potential limitation. In a consecutive examination using a single bronchoscope, the order of the transbronchial approach followed by the transesophageal approach seemed reasonable to minimize the risk of infection; however, it could have affected the accuracy and safety of each procedure. Furthermore, it is well-known that the yield of endoscopic procedures largely depends on the examiner's experience and skill. Our results might not be readily duplicated by less experienced examiners, and better results might be achieved by more skilled examiners. Another limitation was the reliability of the final diagnosis. In the present study, 34 patients had no surgical confirmation of N2 and N3 disease. Thus, the risk exists of inaccuracy if the reference standard is used for referent values. In addition, not all hilar or mediastinal lymph nodes were explored during surgery, which could have led to an overestimation of the endoscopic diagnostic value. However, it would have affected the diagnostic value of each procedure equally; thus, our conclusions regarding the significant superiority of the combined method are well founded.

We, therefore, consider that the combined endoscopic approach with EBUS-TBNA and EUS-FNA with a single bronchoscope is an accurate and safe method for preoperative hilar and mediastinal staging of NSCLC and better than each technique alone.

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EDITORIAL COMMENTARY

Pathologic staging of the mediastinum: When and how?

Jacob A. Klapper, MD, and Chadrick E. Denlinger, MD

Pathologic staging of mediastinal lymph nodes before surgical resection is the accepted standard for patients with non–small cell lung cancer (NSCLC).[1] Mediastinoscopy, endobronchial ultrasound (EBUS), and endoscopic ultrasound are all acceptable means of obtaining tissue. Two prospective studies compared the sensitivity of EBUS with mediastinoscopy among patients with NSCLC and concluded that the 2 modalities are equivalent.[2,3] In the first study patients were randomized to either mediastinoscopy or EBUS followed by mediastinoscopy if EBUS was negative. The sensitivity of mediastinoscopy alone was 79% compared with 85% for EBUS. The addition of mediastinoscopy in patients previously evaluated by EBUS increased the sensitivity to 94%.[2] In the second study, by Yasufuku and colleagues,[3] each patient was evaluated by both EBUS and mediastinoscopy and the sensitivities of the 2 were 81% and 79%, respectively.

The sensitivity of 73% for combined EBUS and endoscopic ultrasound presented by Oki and colleagues[4] in this issue is congruent with prior surgical series where patients went on to resection if the mediastinum was

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Disclosures: Authors have nothing to disclose with regard to commercial support.
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J Thorac Cardiovasc Surg 2014;148:1177-8
0022-5223/$36.00
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http://dx.doi.org/10.1016/j.jtcvs.2014.09.001

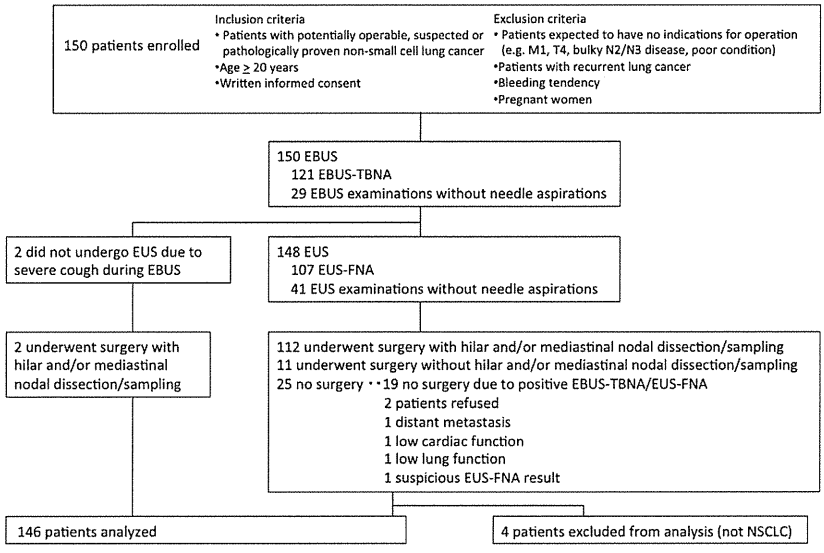

FIGURE E1. CONSORT diagram showing the clinical course of patients enrolled in the study.

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