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Daily Lisinopril vs Placebo for Prevention of Chemoradiation-Induced Pulmonary Distress in Patients With Lung Cancer (Alliance MC1221): A Pilot Double-Blind Randomized Trial

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Abstract

Purpose: Chemoradiation (CRT) is an integral treatment modality for patients with locally advanced lung cancer. It has been hypothesized that current use of an angiotensin-converting enzyme inhibitor during CRT may be protective for treatment-related lung damage and pneumonitis.

Methods and Materials: We conducted a pilot, double-blind, placebo-controlled randomized trial. Study-eligible patients receiving curative thoracic RT were randomly assigned to 20 mg of lisinopril or placebo once daily during and up to 3 months after RT. All patients received concurrent chemotherapy. The primary end point was adverse event profiling. Multiple patient-reported outcome (PRO) surveys, including Lung Cancer Symptom Scale, Function Assessment of Cancer Therapy–Lung, and the EORTC for Lung Cancer Questionnaire (EORTC-QLQ-LC13), were applied with a symptom experience questionnaire. Exploratory comparative statistics were used to detect differences between arms with χ^2 and Kruskal-Wallis testing.

Results: Five institutions enrolled 23 patients. However, accrual was less than expected. Eleven and 12 patients were in the placebo and lisinopril arms (mean age, 63.5 years; male, 62%). Baseline characteristics were balanced. Eighteen patients (86%) were former or current smokers. The primary end point was met; neither arm had grade 3 or higher hypotension, acute kidney injury, allergic reaction (medication-induced cough), or anaphylaxis (medication-related angioedema). Few PRO measures suggested that compared with the placebo arm, patients receiving lisinopril had less cough, less shortness of breath, fewer symptoms from lung cancer, less dyspnea with both walking and climbing stairs, and better overall quality of life (for all, $P < .05$).

Conclusions: Although underpowered because of low accrual, our results suggest that there was a clinical signal for safety—and possibly beneficial by limited PRO measures—in concurrently administering lisinopril during thoracic CRT to mitigate or prevent RT-induced pulmonary distress. Our results showed that a definitive, larger-scale, randomized phase 3 trial is needed in the future. ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01880528) identifier: NCT01880528)

Summary

Previous biologic and clinical evidence has suggested that lisinopril, an angiotensin-converting enzyme inhibitor, may mitigate chemoradiation (CRT)-induced pneumonitis. We conducted a pilot, double-blind, placebo-controlled randomized trial of 23 patients with advanced non–small

cell lung cancer who had concurrent fractionated CRT. They received 20 mg lisinopril or placebo daily during and 3 months after RT. Few patient-reported outcome indices showed that lisinopril was safe, and possibly beneficial, in mitigating RT-induced pulmonary distress, pending further studies.

Keywords

adverse effects; angiotensin-converting enzyme inhibitor; chemoradiation; lisinopril; lung cancer; patient-reported outcome; radiation pneumonitis; randomized; respiratory distress; safety

Introduction

Lung cancer continues to be the most lethal malignancy worldwide and in the United States [1]. Radiotherapy (RT) with or without chemotherapy is an integral part of care in locally advanced cases. Thoracic external beam RT can cause severe respiratory distress and RT-induced pneumonitis. Concurrent chemoradiation is more effective than radiotherapy alone.

Interest has been growing for the use of an angiotensin-converting enzyme (ACE) inhibitor as a possible radioprotectant to prevent or lessen the severity of RT-induced pneumonitis. Many lung cancer patients already have compromised pulmonary function and underlying long-term lung damage from other smoking-related conditions, such as chronic obstructive pulmonary disease. For them, acute RT-induced pneumonitis can be serious and even life-threatening. RT is an integral part of treatment modalities for patients with lung cancer. Because healthy lung tissue is radiosensitive, irradiation to the thorax is limited by accompanied potential adverse effects, such as acute pneumonitis. RT dose is further limited by the use of induction or concurrent chemotherapy, or both, which are pneumotoxic as well. Symptomatic pneumonitis (grade 2) occurs in about 20% of patients with pulmonary and mediastinal irradiation for Hodgkin lymphoma, breast cancer, and lung cancer [2]. Subclinical RT-induced pneumonitis may be underreported.

The need is large and unmet for identification of novel pharmacologic radioprotectors and mitigators such as ACE inhibitors to lessen the potential damage caused by RT-induced pneumonitis. Lisinopril (N²-[(1S)-1-carboxy-3-phenylpropyl]-L-lysyl-L-proline) belongs to a large family of orally available antihypertensive medications, the ACE inhibitors. The target of lisinopril is angiotensin II, an abundant and potent vasoconstrictor in pulmonary tissues. Its proven efficacy is in treatment of hypertension, coronary heart disease, diabetes-related nephropathy, and congestive heart failure. Its common but manageable adverse effects include a characteristic cough, hyperkalemia, and, rarely, medication-induced angioedema. Early laboratory data suggested that biologically, captopril or enalapril decreased morbidities from RT-induced pneumonitis in a rat model [3]. Subsequently, more studies showed histologic evidence of vascular and alveolar improvement and less inflammation in rat-based pneumonitis models treated with ACE inhibitors [4,5]. Studies have also shown that captopril reduced pulmonary endothelial and parenchymal dysfunction [6,7] and delayed late radiation injury to the rat lungs [8].

More recently, a prospective trial by NRG Oncology (formerly the Radiation Therapy Oncology Group [RTOG]) [9] and a large body of evidence from multiple retrospective series [10–16] have shown the potential benefits of ACE inhibitors for this population undergoing RT (including stereotactic body RT). However, before this report, components involving patient-reported outcomes (PROs) had yet to be prospectively evaluated in a multi-institutional clinical trial.

In a pilot, double-blind, placebo-controlled randomized trial, we hypothesized that lisinopril may prevent or alleviate respiratory distress and RT-induced pneumonitis. The enrolled patients underwent standard courses of chemoradiotherapy for lung cancer; both physician-evaluated and patient-reported end points were examined. The trial's purpose was to provide a possible signal if lisinopril may be active compared with placebo in this patient population for mitigation of respiratory distress by RT-induced pneumonitis. The adverse event (AE) profile for both lisinopril and placebo was also evaluated.

Methods and Materials

Trial Design and Patient Selection

The study was approved by the institutional review board at each participating center and all patients provided written informed consent. This was a pilot-based clinical trial endorsed and sponsored by the Alliance for Clinical Trials in Oncology (Alliance MC1221). The basis of this pilot trial design was a phase 1/2 randomized study. The Consolidated Strategy of Reporting Trials flow diagram is shown in the Figure. Eligible patients receiving thoracic RT (45 Gy) for predominantly non-small cell lung cancers were enrolled. An Eastern Cooperative Oncology Group performance score of 2 or better was necessary. The use of concurrent chemotherapy was optional per protocol; nevertheless, all 23 enrolled and randomly assigned patients had been planned for and given concurrent chemotherapy. Age (<70 years vs ≥70 years) was considered as a stratification factor. Other inclusion criteria required that the patient be age 18 years or older with a histologic confirmation of non-small cell carcinoma of the lung.

The following laboratory criteria needed to be met for each patient: absolute neutrophil count $\geq 1,500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, hemoglobin $\geq 9.0 \text{ g/dL}$, and creatinine clearance $\geq 30 \text{ mL/min}$ by Cockcroft-Gault formula. Reference potassium and sodium values were also required. Importantly, an initial physical examination was needed with systolic blood pressure $\geq 100 \text{ mm Hg}$ and diastolic blood pressure $\geq 60 \text{ mm Hg}$. Women of childbearing age were required to have a negative pregnancy test. Each patient needed to be able to complete PRO questionnaires either alone or with assistance.

Exclusion criteria included severe comorbid systemic illnesses that, in the judgment of the investigator, would classify the patient as inappropriate for the trial. Uncontrolled intercurrent illness included symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, severe psychiatric illness, and other active malignancy (excluding nonmelanotic skin cancer) 3 years or less before trial registration. Trial criteria did not allow a history of myocardial infarction 6 months or less before registration or severe congestive heart failure with ventricular arrhythmia. The patient could not have a history of prior RT to

the thorax. Finally, patients were excluded if they had existing contraindications to ACE inhibitors, such as hypersensitivity, bilateral renal artery stenosis, angioedema, or previous adverse drug reaction. Use of ACE inhibitors (including lisinopril) or ACE receptor blockers 90 days or less before registration, usually for another medical condition, was not allowed.

Study Intervention and PRO Questionnaires

At the beginning of CRT, the patients were randomly assigned to receive either 20 mg of lisinopril (10 mg for the initial 7 days and then titrated to 20 mg) or placebo once daily during RT and up to 3 months post RT. Patients were monitored weekly during RT and at 1 month and 3 months post RT. Questionnaires for PROs were administered on the same schedule for both groups and included Lung Cancer Symptom Scale (LCSS), Symptom Experience Questionnaire (SEQ), EORTC for Lung Cancer Questionnaire (EORTC-QLQ-LC13), and Function Assessment of Cancer Therapy–Lung (FACT-L). The LCSS tool contains 6 major symptoms associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global quality of life (QOL). Specific patient- and treatment-related QOL items were assessed with EORTC-QLQ-LC13 and FACT-L questionnaires. The EORTC-QLQ-LC13 is a clinically valid, 13-question module containing measures of lung cancer–associated symptoms and also adverse effects from conventional chemotherapy and RT [17]. The validated FACT-L is a 9-question lung cancer–specific symptom scale administered in conjunction with the Function Assessment of Cancer Therapy-General, which contains physical, social, emotional, and functional subscales [18]. AEs were collected at baseline, weekly during RT, and at 3 months post RT.

Statistical Methods

This trial focused on generating pilot information that may inform the conception of a larger future trial. The sample size was determined by logistical considerations, rather than based on a formal hypothesis testing of the primary end point, and any statistical hypothesis testing was regarded as exploratory. Descriptive data analysis took place after the trial was closed and follow-up for all patients was completed. No adjustment for multiple comparisons was made as a result.

Primary End Point

The primary goal was to assess the AE profile of lisinopril therapy in this patient population. The primary end point was the incidence of, regardless of attribution, grade 3 or higher hypotension, acute kidney injury, allergic reaction, or anaphylaxis as measured using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 scale during and up to 3 months post RT. Descriptive statistics of frequency (percentage) were used to summarize AE incidence and severity; χ^2 testing was performed in an exploratory manner.

Secondary PRO End Points

LCSS, FACT-L, and EORTC-QLQ-LC13 were scored according to their respective scoring algorithms, and patient scores were converted to point scales of 0 to 100, where 100 was best QOL. The transformation allowed for direct comparability between scale scores of differing ranges. Compared with the primary end point, at any time point of the trial, patient-

reported acute respiratory distress (dyspnea) was measured with use of the maximum score of the shortness of breath question on the LCSS [19]. Descriptive statistics (frequencies in percentage, mean, SD, and 95% CI) were compiled for PRO scores, individual questions, and SEQ symptoms. Differences between the 2 arms were compared using 2-sample *t* tests or Wilcoxon rank sum tests. Missing data were examined graphically, and simple correlation was applied to determine any associations with baseline patient characteristics, risk factors, PRO scores, and missing PRO scores.

Sample Size

As per study design, the sample size was originally set at 50 patients for both arms. For sample size estimation, it was assumed that the placebo arm had a 90% success rate (ie, a 10% chance of a grade 3 or higher toxicity). With 50 patients (25 patients per treatment group), the precision estimates based on a 2-sided test of equal proportions with α of .05. The trial was monitored by the institutional data safety monitoring board at each participating medical center, and a stopping rule was in place to monitor patient safety in regard to AEs (Supplementary Table 1). Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center; data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. Results analyzed were available in our database as of April 30, 2016, after the follow-up period was completed for all patients in both arms.

Results

Five institutions enrolled 23 patients into the trial, with 1 institution recruiting 16 patients (70%). Eleven and 12 eligible patients were in the placebo and lisinopril arms, respectively. Because of less-than-expected accrual, the trial recruitment stopped early with enrollment of the 23 patients. As a result, *P* values could not accurately reflect a truly powered test as originally intended and were not definitive, thus any significant results reported should be interpreted as exploratory.

All baseline characteristics were balanced, including chronic obstructive pulmonary disease status, smoking history, and amount of lung irradiated which was measured by V20Gy in percentage (Table 1). All patients in both arms received concurrent platin-based doublet chemotherapy. Mean age was 63.5 years; 13 patients (62%) were male. Eighteen patients (86%) were former or current smokers.

For our primary end point, neither arm had a grade 3 or higher hypotension, acute kidney injury, allergic reaction (ie, medication-induced cough), or anaphylaxis (medication-related angioedema) during and up to 3 months following RT (Table 2). The incidences of grade 2 hypotension were 2 vs 4 patients for placebo and lisinopril, respectively ($P=.26$). As measured by worst dyspnea score on the LCSS, acute respiratory distress was more severe in placebo patients than lisinopril patients (mean [SD], 42.0 [27.8] vs 77.5 [23.8]; $P=.006$). A higher score reflected less pulmonary distress in this scale and greater quality of life.

One patient taking lisinopril had grade 2 acute kidney injury ($P=.20$). One patient had grade 4 dyspnea in the placebo arm. On data examination from the Adverse Event Reporting

System, we found that this patient had severe chronic obstructive pulmonary disease and long-term oxygen use at baseline. In fact, at that time, the study arm was unblinded, and the patient began lisinopril treatment clinically as recommended by his treating oncologist; he received antibiotics for pneumonia as well. No patient had grade 5 toxicity.

The PRO analyses for SEQ (Supplementary Table 2), LCSS (Table 3), EORTC-QLQ-LC13 (Table 4), and FACT-L (Table 5) surveys are reported. Selected PRO results from LCSS (Supplementary Figure A1 and A2), EORTC (Supplementary Figure B1 and B2), and FACT (Supplementary Figure C1 and C2) surveys were also temporally plotted for the arms, respectively. All baseline PRO results were balanced except for more shortness of breath in the placebo arm, reported with SEQ and LCSS, and less dyspnea symptoms in climbing stairs in the lisinopril arm, reported with EORTC-QLQ-LC13. With a number of PRO measures, limited observations suggested that patients taking lisinopril may have better QOL and cardiopulmonary reserve (than placebo patients) during RT and medication use periods (Tables 3–5). Similarly, exploratory analyses of the SEQ results showed that there was more shortness of breath during exercise and increased heart rates for patients taking placebo at the last RT cycle (both $P<.02$) (Supplementary Table 2). At week 4, the lung cancer symptom subscale and total LCSS scores appeared to be higher for patients taking lisinopril, along with a number of individual PRO values, including cough and shortness of breath and symptoms from lung cancer, that appeared to favor lisinopril (all $P<.04$) (Table 3). In EORTC-QLQ-LC13 and over a few time points (although not all), including maximum QOL score over the study period, patients taking lisinopril appeared to have better scores for dyspnea with walking and climbing stairs (all $P .02$) (Table 4). Finally, with the FACT-L surveys, lisinopril-treated patients seemed to enjoy higher levels of social and family functional well-being, higher levels of lung-specific symptom subscale, and higher overall scores at selected time points (all $P<.05$) (Table 5). The rest of the PRO indices did not show any clinically meaningful differences between the lisinopril and placebo arms.

Discussion

We report the results of a randomized, placebo-controlled pilot trial for measuring the effect of lisinopril, an ACE inhibitor, on pulmonary distress of patients receiving daily thoracic RT concurrent with platin-based doublet chemotherapy. With CTCAE, we demonstrated that oral lisinopril at 20 mg daily was safe to use in a lung cancer population undergoing intensive CRT. It did not seem to lead to undesired hypotension, renal injuries, or medication-related allergic reaction and anaphylaxis; however, the results should be validated in a larger, randomized trial that also involves more robust end points to test efficacies.

In this pilot trial, in an exploratory manner, we tested a number of PRO measures for respiratory distress and demonstrated that, across a few end points with LCSS, EORTC-QLQ-LC13, and FACT-L surveys, statistically significant differences may exist favoring the use of lisinopril in this population. These differences showed that improved respiratory symptoms and less RT-associated lung problems for patients undergoing thoracic RT may be possible with lisinopril over placebo. However, the results were not definitive because our pilot study was underaccrued. The study was conducted under a pilot mechanism that

encompassed features of both phase 1 and randomized phase 2 studies. This design was ideal at the time of trial conception because we were potentially testing the use of a cardiovascular medication in a group of patients with lung cancer with **normotensive** blood pressures and evaluating whether probable signals of efficacy might exist against placebo.

Lisinopril has been an ideal agent to test for mitigation of RT-induced pneumonitis. Compared with its prototype captopril, lisinopril is hydrophilic and has a longer biologic half-life and better tissue penetration in the body. Lisinopril also doses easily with a schedule of once daily by mouth. Hypotension is a potential AE for antihypertensive medications such as lisinopril. Acute kidney injury may result as a complication of lisinopril use because of its vascular effects on afferent and efferent renal arterioles. Allergic reaction or anaphylaxis, such as acute swelling of the face and trunk and including angioedema, is a rare but possible AE associated with first-time lisinopril use. In our study, we noted that while none of the patients in either arm had any allergic reaction (including lisinopril-induced cough) or anaphylaxis toward the medication, hypotension and acute kidney injury could still be common in a group of lung cancer patients who were actively getting intensive radiotherapy or chemoradiation for their treatments. However, overall, patients in the lisinopril arm did not statistically have more hypotension or acute kidney injury than the placebo arm. These findings should be validated in a larger randomized trial in the future.

Prospectively, the NRG Oncology group in 2016 issued its final report from the RTOG 0123 trial [9]. Although their accrual target was not met (33 patients were allotted to treatment arms; target sample size, 205 patients), the safety of ACE inhibitor treatment of lung cancer patients was similarly suggested. The incidences of grade 2+ RT-related pulmonary toxicity were 23% and 14% for the observation and captopril arms, respectively (*P* not reported). The authors of the report urged testing of newer-generation ACE inhibitors, which was subsequently attempted in the present trial. Another prospectively randomized trial of 55 patients also showed statistical trends of captopril improving the rates of RT and pulmonary-related injuries and possibly death in the setting of total body RT [20].

In the past few years, we have started to see a large number of positive retrospective series across multiple institutions in lung cancer patients who underwent treatment with either conventionally fractionated RT [10,11,15] or stereotactic body RT [12–14,21]. These studies have consistently reported the efficacy and safety of (often incidental) concurrent ACE inhibitor use, suggesting that the use of lisinopril or other ACE inhibitors may be beneficial for patients receiving active thoracic RT treatments. Our prospective results added to this existing body of evidence for lisinopril. However, a larger, definitive trial is still lacking presently. The pharmacologic class of angiotensin receptor blockers should also be explored.

The introduction of multiple PRO survey tools was important for this patient population with lung cancer. The PRO surveys focus on the patient's comprehensive experience living with cancer and undergoing treatments, instead of solely evaluating a mechanistic definition of RT-induced lung injury, including pneumonitis, with CTCAE criteria. Recently, patient-centered, adaptively PRO-driven clinical interventions even improved overall survival in a large-scale randomized trial with 766 patients [21]. Experienced daily by our patients with lung cancer, serious impairments and physiologic impacts, such as nausea, vomiting, cough,

shortness of breath, dyspnea, pain, and fatigue, are often combined with prevalent distressed feelings of anxiety, situational depression, and a disruption of familial and social relationships, which have been understudied in the thoracic literature [22,23]. The selected survey tools, including LCSS [19], EORTC-QLQ-LC13 [17], and FACT-L [18], were among the most common that have been systematically reviewed with investigator's confidence, validated framework, and proper psychometric properties [23]. Our trial thus represented one of the early efforts in adopting PRO surveys as parts of end points in the new generation of symptom control studies for modern eras in thoracic oncology, although unfortunately it was limited by low patient accrual.

In addition to recognizing the pulmonary risks due to thoracic RT, it is important to acknowledge that RT-associated cardiac comorbidities also have an important role in lung cancer patient outcome [2,24]. Our PRO data may provide a glimpse of this phenomenon; yet, the level of evidence was limited to only hypothesis generation at this time. Patients were noted to have less bothering palpitation due to tachycardia during the last RT cycle when taking lisinopril vs placebo ($P<.01$); however, the significance of this is uncertain (Supplementary Table 2). Future trial efforts will need to capture the potential cardiopulmonary benefits brought forward by ACE inhibitors or ACE receptor blockers because the renin-angiotensin-aldosterone regulatory system has significant cardiac influences physiologically. Biomarker analyses such as Galectin-3, B-type natriuretic peptide, transforming growth factor- β , and other molecular correlations are encouraging topics for future research [8,25].

Limitations

Our study has a number of limitations that must be taken into account when interpreting our data and conclusions. First, despite multiple efforts and extensions of the trial's accrual period, we were not able to meet our goal of 50 patients. Only 23 of a planned 50 patients were eventually enrolled. Thereby, the anticipated power that was estimated initially was diminished. Previously, the RTOG 0123 trial also concluded with difficulties completing their trial with expected accrual numbers, further highlighting the fact that stronger and more enthusiastic efforts are needed in motivating medical centers and patients to participate in symptoms control trials for thoracic malignancies. More effort needs to be made for understanding why this type of trial may not accrue as robustly, and documentation of prescreened failure reasons can be helpful. Further funding opportunities with longer periods of time for support may be necessary in the future, with the involvement of more clinical centers of excellence, including our community hospital partners. Second, although the trial was randomized, we noticed a slight imbalance in 3 PRO items at baseline, favoring the lisinopril group (likely due to the small patient numbers), which was consistent across surveys (namely, shortness of breath in SEQ at rest and in LCSS during exercise, and dyspnea with stair climbing in EORTC). In the final analyses, this probable beneficial difference persisted. There were 2 possibilities: the use of lisinopril may have augmented this difference, suggestive that lisinopril could be active in alleviating pulmonary distress, and this could be by chance. Without a definitive trial in the future, it will be difficult to conclude. Third, a number of our patients still had cough as a result of coexisting morbidities, lung cancer, or its associated treatments, and the present study was not designed

to elucidate whether lisinopril may be a confounding factor. Our trial showed that PRO data in the pilot trial setting could be used to test the use of ACE inhibitors for lung cancer patients undergoing thoracic CRT.

Conclusions

Although underpowered, results from this trial have provided a possible signal for safety and suggested probable efficacy, by PRO measures, in concurrently administering lisinopril for patients with advanced lung cancer who require fractionated CRT-based treatments. Use of lisinopril for mitigation or prevention of RT-induced pulmonary distress or pneumonitis will require further investigation. The planning of a larger-scale randomized phase 3 trial is urgently needed as a result.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACE	angiotensin-converting enzyme
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EORTC-QLQ-LC13	EORTC for Lung Cancer Questionnaire
FACT-L	Function Assessment of Cancer Therapy–Lung
LCSS	Lung Cancer Symptom Scale
PRO	patient-reported outcome QOL, quality of life
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group

SEQ

Symptom Experience Questionnaire

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Figure.

Consolidated Standards of Reporting Trials Flow Diagram for the MC1221 (Alliance for Clinical Trials in Oncology) Lisinopril vs Placebo Trial. This randomized trial evaluated lisinopril use vs placebo during radiotherapy for patients with locally advanced lung cancer.

^a Evaluable for primary end point. ^b One evaluable for primary end point. AE indicates adverse event.

Table 1.**Baseline Patient and Treatment Characteristics**

Characteristics ^a	Trial Arm		P Value	Statistical Test ^b
	Lisinopril (n=11)	Placebo (n=10)		
Age, median (range), y	62.0 (49.0–87.0)	62.0 (54.0–83.0)	.86	1
Age, 70 y	2 (18)	2 (20)	.92	2
Race/ethnicity			.28	2
White	11 (100)	9 (90)		
Nonwhite	0 (0)	1 (10)		
Sex			.47	2
Male	6 (55)	7 (70)		
Female	5 (45)	3 (30)		
Systolic blood pressure, mean (SD), mm Hg	131 (24)	128 (10)	.74	1
Diastolic blood pressure, mean (SD), mm Hg	74 (9)	78 (10)	.50	1
COPD status			.87	2
Not diagnosed/no COPD	8 (73)	6 (60)		
Mild/moderate	1 (9)	2 (20)		
Severe/oxygen-dependent	2 (18)	2 (20)		
Cigarette use			.51	2
Never smoker	2 (18)	1 (10)		
Former smoker	8 (73)	9 (90)		
Current smoker	1 (9)	0 (0)		
Cigarette pack-years, mean (SD)	47.6 (30.0)	56.9 (42.4)	.77	1
Concurrent chemotherapy			.47	2
Cisplatin/etoposide	6 (55)	5 (50)		
Carboplatin/paclitaxel	3 (27)	5 (50)		
Carboplatin/pemetrexed	2 (18)	0 (0)		
Total lung volume receiving 20 Gy, V20Gy % ^c			.62	2
20.0%–27.4%	7 (64)	7 (70)		
27.5%–34.9%	3 (27)	3 (30)		
35%	1 (9)	0 (0)		

Abbreviation: COPD, chronic obstructive pulmonary disease.

^aValues are shown as number (percentage) of patients unless stated otherwise.

^bOne refers to Kruskal-Wallis test; 2, Fisher exact test.

^cMeasurement of amount of irradiated lung, by percentage, that received 20 Gy of radiotherapy or more.

Table 2.

Adverse Effects Between Arms* (Primary End Point)

Adverse Effect, Maximum Grade ^a	Trial Arm, No. (%)		P Value ^b
	Lisinopril (n=11)	Placebo (n=10)	
Hypotension			.26
0	7 (64)	6 (60)	
1	0 (0)	2 (20)	
2	4 (36)	2 (20)	
Acute kidney injury			.20
0	8 (73)	10 (100)	
1	2 (18)	0 (0)	
2	1 (9)	0 (0)	
Allergic reaction			
0	11 (100)	10 (100)	N/A
Anaphylaxis			
0	11 (100)	10 (100)	N/A

Abbreviation: N/A, not applicable.

* During and up to 3 months following radiotherapy.

^aNo patient had any grade 3+ adverse effect of hypotension, acute kidney injury, allergic reaction, or anaphylaxis due to study drugs.^bWith χ^2 test.

Table 3. LCSS Comparison Between Lisinopril (L) and Placebo (P) Use in MC1221 (Alliance for Clinical Trials in Oncology), for All Patients

Characteristic	Value at Time Point in Trial ^{d,b}																	
	Baseline			Week 1			Week 2			Week 3			Week 4			Week 5		
	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d
Good appetite	87.8	69.0	.11	58.2	66.0	.43	82.2	66.7	.10	66.7	66.7	.96	77.5	55.6	.12	68.3	74.3	.83
Fatigue	72.2	66.0	.56	52.7	48.0	.77	65.6	61.1	.65	58.9	64.4	.53	63.8	52.2	.33	55.0	62.9	.51
Cough	90.0	78.0	.09	82.7	66.0	.03	77.8	76.7	>.99	78.9	64.4	.13	86.3	63.3	.02	90.0	75.7	.36
Shortness of breath	96.7	60.0	<.01	91.8	70.0	.01	98.9	76.7	.01	94.4	73.3	.05	97.5	71.1	.01	88.3	67.1	.11
Lack of bloody sputum	97.8	98.0	.94	98.2	100.0	.34	97.8	95.6	.94	96.7	98.9	.94	98.8	100.0	.29	100.0	100.0	>.99
Pain	71.1	79.0	.83	76.4	84.0	.85	81.1	82.2	.64	84.4	86.7	.69	86.3	72.2	.48	81.7	78.6	.94
Lung cancer symptom subscale	82.7	75.0	.41	76.7	72.3	.48	83.9	76.5	.17	80.0	75.7	.60	85.0	69.1	.03	80.6	76.4	.83
Symptoms from lung cancer	86.7	76.0	.30	93.6	80.0	.04	93.3	71.1	.03	88.9	75.6	.16	96.3	71.1	.02	93.3	77.1	.09
Activity impairment	72.2	61.0	.48	82.7	69.0	.22	81.1	68.9	.15	83.3	65.6	.13	77.5	64.4	.38	80.0	65.7	.27
Self-rated QOL today	72.2	70.0	.80	70.9	57.0	.37	75.6	60.0	.21	64.4	61.1	.75	70.0	48.9	.12	70.0	61.4	.66
Total LCSS score	79.4	73.0	.47	78.6	71.1	.26	83.7	73.2	.09	79.6	73.0	.35	83.8	66.5	.02	80.7	73.7	.78

Abbreviations: LCSS, Lung Cancer Symptom Scale; QOL, quality of life.

^aReports mean; statistically significant *P* values are bolded.

^bHigher values reflect better QOL.

^cNumber of patients at week 6 was small for both L (n=5) and P (n=5) arms.

^dKruskal-Wallis test.

EORTC-QLQ-LC13 Comparison Between Lisinopril (L) and Placebo (P) Use in MC1221 (Alliance for Clinical Trials in Oncology), for All Patients

Table 4.

Characteristic	Value at Time Point in Trial ^{a,b}																	
	Baseline			Week 1			Week 2			Week 3			Week 4			Week 5		
	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d
Cough	73.3	60.0	.17	81.8	63.3	.09	70.4	66.7	.69	74.1	56.7	.07	75.0	55.6	.07	83.3	66.7	.24
Lack of coughing up blood	96.7	93.3	.54	100.0	100.0	>.99	100.0	92.6	.32	100.0	96.7	.34	95.8	100.0	.29	100.0	100.0	>.99
Dyspnea at rest	96.7	76.7	.11	100.0	90.0	.06	100.0	88.9	.15	100.0	93.3	.34	100.0	85.2	.08	94.4	85.7	.56
Dyspnea when walking	86.7	56.7	.06	93.9	66.7	.01	96.3	77.8	<.05	92.6	60.0	.01	95.8	66.7	.01	83.3	61.9	.17
Dyspnea when climbing stairs	90.0	50.0	<.01	81.8	53.3	>.05	91.7	66.7	.02	77.8	43.3	.03	83.3	51.9	.04	66.7	47.6	.35
Lack of sore mouth/tongue	100.0	100.0	>.99	97.0	80.0	.10	96.3	77.8	<.05	96.3	80.0	.07	100.0	85.2	.08	77.8	81.0	.57
Swallowing problems	100.0	93.3	.32	90.9	83.3	.79	66.7	74.1	.57	66.7	66.7	.90	79.2	63.0	.41	66.7	52.4	.62
Hand/feet tingling	96.7	76.7	.11	93.9	90.0	.84	92.6	81.5	.29	96.3	81.5	.22	95.8	77.8	.07	94.4	81.0	.29
Hair loss	96.7	100.0	.32	97.0	96.7	.94	81.5	92.6	.29	59.3	73.3	.51	62.5	63.0	.65	50.0	71.4	.18
Chest pain	90.0	80.0	.35	87.9	76.7	.23	81.5	81.5	.84	81.5	83.3	.88	91.7	81.5	.36	83.3	76.2	.53
Arm/shoulder pain	86.7	93.3	.54	90.9	76.7	.12	96.3	74.1	.04	92.6	70.4	.21	91.7	74.1	.26	100.0	81.0	.08
Other body pain	73.3	74.1	.92	87.9	73.3	.16	81.5	66.7	.25	88.9	70.0	.17	79.2	81.5	.86	88.9	81.0	.62
Pain relief with use of medications	20.0	38.9	.19	0.0	38.1	.16	46.7	46.7	.91	60.0	26.7	.10	16.7	40.0	.31	6.7	0.0	.47

Abbreviation: EORTC-QLQ-LC13, EORTC for Lung Cancer Questionnaire.

^aReports mean; statistically significant *P* values are bolded.

^bHigher values reflect better quality of life.

^cNumber of patients at week 6 was small for both L (n=5) and P (n=4) arms.

^dKruskal-Wallis test.

FACT-L Comparison Between Lisinopril (L) and Placebo (P) Use in MC1221 (Alliance for Clinical Trials in Oncology), for All Patients

Table 5.

Value at Time Point in Trial ^{a,b}																			
Baseline				Week 1				Week 2				Week 3				Week 4			
Characteristic	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L	P	P Value ^d	L
Total physical	81.2	72.1	.20	76.0	67.9	.26	76.6	69.0	.56	76.6	71.1	.77	76.3	63.1	.44	76.2	68.4	.57	81.4
Total social/family	90.8	79.9	.16	82.6	77.3	.27	90.8	75.3	<.05	95.1	77.4	.01	91.4	71.9	.03	94.7	77.8	.10	93.8
Total emotional	61.9	62.5	.94	71.6	67.9	.30	73.6	72.7	.50	75.5	67.1	.21	72.9	69.3	.56	70.8	68.5	.72	73.3
Total functional	67.5	55.7	.26	68.5	56.4	.29	75.0	64.7	.21	71.4	59.3	.25	69.6	56.7	.27	78.0	61.2	.19	73.6
FACT-L specific	76.8	62.9	.07	76.0	66.7	.17	77.8	71.8	.45	82.5	66.1	.02	83.0	63.3	.01	77.4	65.3	.20	75.7
FACT-G overall	75.4	67.6	.26	74.7	67.4	.16	79.0	70.4	.15	79.6	68.7	.09	77.6	66.0	.17	79.9	69.0	.20	80.5
FACT-L overall	74.2	66.6	.33	74.9	68.5	.16	78.8	70.7	.17	80.2	68.2	.05	78.7	67.1	.20	79.4	68.2	.17	79.6
Trial outcome index score	73.6	63.6	.24	73.5	63.4	.16	76.5	68.5	.35	76.9	65.5	.19	76.3	60.0	.09	77.2	65.0	.25	76.9

Abbreviations: FACT-G, Function Assessment of Cancer Therapy–General; FACT-L, Function Assessment of Cancer Therapy–Lung.

^aReports mean; statistically significant *P* values are bolded.

^bHigher values reflect better quality of life.

^cNumber of patients at week 6 was small for both L (n=5) and P (n=5) arms.

^dKruskal-Wallis test.