

Decreased Risk of Radiation Pneumonitis With Coincident Concurrent Use of Angiotensin-converting Enzyme Inhibitors in Patients Receiving Lung Stereotactic Body Radiation Therapy

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Objectives: Angiotensin-converting enzyme inhibitors (ACEi) have demonstrated decreased rates of radiation-induced lung injury in animal models and clinical reports have demonstrated decreased pneumonitis in the setting of conventionally fractionated radiation to the lung. We tested the role of ACEi in diminishing rates of symptomatic (grade ≥ 2) pneumonitis in the setting of lung stereotactic body radiation therapy (SBRT).

Methods: We analyzed patients treated with thoracic SBRT to 48 to 60 Gy in 4 to 5 fractions from 2006 to 2014. We reviewed pretreatment and posttreatment medication profiles to document use of ACEi, angiotensin receptor blockers, bronchodilators, aspirin, PDE-5 inhibitors, nitrates, and endothelin receptor antagonists. Pneumonitis was graded posttreatment based on Common Terminology Criteria for Adverse Events Version 4.0. Univariate and multivariate analysis was performed and time to development of pneumonitis was evaluated by the Kaplan-Meier method.

Results: A total of 189 patients were evaluated with a median follow-up of 24.8 months. The overall 1-year rate of symptomatic pneumonitis was 13.2%. The 1-year rate of symptomatic pneumonitis was 4.2% for ACEi users versus 16.3% in nonusers ($P=0.03$). On univariate analysis, the odds of developing grade 2 or greater pneumonitis were significantly lower for patients on ACEi ($P=0.03$). On multivariate analysis, after controlling for clinicopathologic characteristics and dosimetric endpoints, there was a significant association between ACEi use and decreased risk of clinical pneumonitis ($P=0.04$). Angiotensin receptor blockers or other bronchoactive medications did not show significant associations with development of pneumonitis.

Conclusions: Incidental concurrent use of ACEi demonstrated efficacy in diminishing rates of symptomatic pneumonitis in the setting of lung SBRT.

Key Words: lung SBRT, lung toxicity, pneumonitis, ACE inhibitors
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The clinical application of stereotactic body radiation therapy (SBRT) for the treatment of lung tumors in the setting of early-stage lung cancer and oligometastatic disease has been expanding for the past 10 years.¹ Normal tissue response of the lung to radiation is an important limiting factor in treating lung cancer, especially in the clinically relevant nonoperable patient population for which SBRT is currently most utilized.^{2–4} Advanced stages of coincident lung disease, often from chronic obstructive pulmonary disease and other comorbid conditions, may preclude surgery in these patients, and at the same time can predispose to radiation-induced lung toxicity. Angiotensin-converting enzyme inhibitors (ACEi) have been shown to mitigate radiation-induced lung injury in several preclinical animal models.^{5–8} The retrospective clinical experience in the setting of conventionally fractionated radiotherapy and concurrent chemotherapy and radiotherapy has been mixed, with several reports demonstrating decreased pneumonitis and 1 report finding no difference.^{9–12} The Radiation Therapy Oncology Group undertook a phase II trial to test this effect with the ACEi captopril. This study unfortunately closed early due to poor accrual.¹³ The role of ACEi in abrogating lung toxicity in the setting of SBRT remains unclear, with 1 recent report demonstrating benefit.¹⁴ The objective of this study was to evaluate the role of concurrent incidental use of ACEi at preventing symptomatic acute lung toxicity in the setting of thoracic SBRT.

METHODS

Our institutional database was analyzed to identify patients treated with thoracic SBRT for either radiographically or pathologically confirmed lung cancer or oligometastases from 2006 to 2014. Study design and development were approved by our institutional review and privacy boards (IRB Number LU205020).

Patients were treated with doses of 48 to 60 Gy in 4 to 5 fractions, prescribed to the 70% to 100% isodose volume. Patients receiving SBRT with alternative fractionation schemes and to lower doses were excluded. We only included those patients with at least 1 follow-up visit posttreatment. Patients were simulated with 4-dimensional computed tomography scan utilizing respiratory imaging and synchronization through Real-time Position Management System (Varian Oncology, Palo Alto, CA). Internal target volume (ITV) was delineated incorporating maximum inspiratory, maximum expiratory, and maximum intensity projection of the computed tomography data. A uniform 5 mm planning target margin was placed around the ITV to generate planning target

volume. Further motion management with abdominal compression or respiratory gating was utilized at the physician's discretion. All plans were evaluated to meet predefined dosimetric criteria according to institutional policy, adhering to previous published reports for acceptable lung, heart, spinal cord, and esophagus.¹⁵ Three-dimensional conformal technique, static intensity-modulated radiation therapy, or volumetric-modulated arc therapy were used for treatment delivery.

Pneumonitis toxicity was graded according to the Common Terminology Criteria for Adverse Events version 4.0 (Table 1).¹⁶ Pretreatment and posttreatment medication profiles were reviewed to document concurrent use of ACEi, angiotensin receptor blockers, bronchodilators, aspirin, phosphodiesterase-5 inhibitors, nitrates, and endothelin receptor antagonists. These medications were chosen due to known either anti-inflammatory and/or bronchoactive effects. Phosphodiesterase-5 inhibitors were chosen due to their increased use for pulmonary hypertension. Other clinical parameters collected included age, stage, previous thoracic radiation therapy, and smoking status. Dosimetry was available for evaluation in 136 (71%) of patients. We collected plan and dosimetric data including for total lung volume-ITV, the V20 (volume of lung receiving ≥ 20 Gy), V12.5 (volume of lung receiving ≥ 12.5 Gy), V5 (volume of lung receiving ≥ 5 Gy), and mean lung dose (MLD).

Statistics

Univariate analysis was performed with Fisher exact test and χ^2 analysis for categorical variables and Student *t* test and Wilcoxon rank-sum test for continuous variables. Age, Karnofsky performance status, dose, and dosimetric endpoints were compared as continuous variables. We created a multivariable model by including all of the variables with a univariable significance <0.2 . Because dosimetric endpoints of V20, V12.5, V5, and MLD track together, we evaluated them 1 at a time and selected the best predictor based on model fit, utilizing Akaike Information Criterion. We then entered all selected variables into the model at the same time and removed any with significance >0.2 to create the final model. Multivariate analysis was conducted with adjusted logistic regression model used to calculate odds ratios for a categorical comparison with correction applied to resolve zero cell observations.¹⁷ Kaplan-Meier method was used to calculate time to grade 2 pneumonitis and log-rank test was used to compare treatment groups. Analysis was conducted using

R Version 3.2.2 (Vienna, Austria) and SAS version 9.4 (Cary, NC).

RESULTS

A total of 189 patients met inclusion criteria and were analyzed. The median follow-up for the entire cohort was 24.8 months. The majority (87.8%) of patients were treated with 50 Gy in 5 fractions, and 9.5% of patients with 60 Gy in 5 fractions. Forty-nine (26%) were found to be incidentally prescribed an ACEi class of medication before delivery of SBRT, with the majority (80%) being on subclass agent lisinopril. Table 2 summarizes baseline treatment, patient, and clinical characteristics and medication profiles.

In the entire population, 25 patients experienced grade 2 or higher pneumonitis, which included 21 grade 2, 3 grade 3, and 1 grade 4 toxicity, with a 1-year rate of symptomatic pneumonitis of 13.2%. The median time of onset to RP was 4.8 months (range, 0.6 to 12 mo). Only 2 patients on a concurrent ACEi experienced symptomatic pneumonitis. The 1-year rate of symptomatic pneumonitis was 4.2% in the ACEi users versus 16.3% in nonusers ($P=0.03$). On univariate analysis, there was a significant difference from the expected frequencies for ACEi and grade 2 pneumonitis ($P=0.03$) (Table 3). The odds of developing grade 2 pneumonitis while on an ACEi was 0.22 (95% CI, 0.05-0.95) compared with patients not on an ACEi. Kaplan-Meier analysis demonstrated statistically significant freedom from grade 2 pneumonitis in the ACEi group (log-rank $P=0.03$) as shown in Figure 1. For other variables investigated, use of aspirin also showed a trend toward decreased risk of development of RP but this was not significant on univariate analysis ($P=0.17$). Patients using concurrent bronchodilators showed increased risk for development of symptomatic pneumonitis on univariate ($P=0.07$) and multivariate analysis ($P=0.04$).

There was a significant difference from the expected frequencies for sex and grade 2 pneumonitis ($P=0.04$) (Table 4). There was also a significant association between the number of fractions and development of grade 2 pneumonitis; patients developing symptomatic pneumonitis had significantly fewer fractions than those who did not ($P=0.008$), although very few patients in this study received <5 fractions. Patients developing clinical pneumonitis all had higher V20, V12.5, V5, and MLD, but differences for these endpoints did not reach statistical significance. Tumor location (upper lobes vs. lower/middle lobes vs. multiple lobes) also was not associated with increased risk of pneumonitis ($P=0.36$). Pretreatment diagnosis of pulmonary fibrosis was recorded in 6 patients and did not predispose to development of pneumonitis (Table 4).

On multivariate analysis, there was a significant association between incidental ACEi use and decreased risk of developing symptomatic pneumonitis after controlling for sex, number of fractions, dosimetric factors, aspirin use, and bronchodilator use ($P=0.04$) (Table 5). Patients taking an ACEi were almost 6 times less likely to develop grade 2 or greater pneumonitis than patients not taking an ACEi (odds ratio = 0.17; 95% CI, 0.03-0.89).

DISCUSSION

In our analysis, ACEi use seems to have efficacy at diminishing rates of symptomatic pneumonitis in the setting of lung SBRT, which was an independent effect when controlling for clinicopathologic characteristics and dosimetric endpoints. Other bronchoactive medications did not demonstrate protective effects, notably no improvement was seen with

TABLE 1. Posttreatment Pneumonitis Grading System (NCI CTCAE v4.0)

| | |
|---|--|
| Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma | |
| Grade 1 | Asymptomatic; clinical or diagnostic observations only; intervention not indicated |
| Grade 2 | Symptomatic; medical intervention indicated; limiting Instrumental Activities of Daily Living (ADL)* |
| Grade 3 | Severe symptoms; limiting self-care ADL†; oxygen indicated |
| Grade 4 | Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation) |
| Grade 5 | Death |

*Instrumental Activities of Daily Living refers to activities such as preparing meals, shopping for groceries or clothes, using the telephone, managing money.

†Self-Care Activities of Daily Living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

TABLE 2. Basic Patient Characteristics

| Patient and Tumor Characteristics | Entire Cohort | ACEi Users | Nonusers |
|---|---------------|------------|------------|
| Patients | 189 | 49 | 140 |
| Age (y) | | | |
| Median | 71 | 74 | 71 |
| Range | 29-90 | 53-90 | 29-90 |
| Karnofsky performance status | | | |
| Median | 80 | 80 | 80 |
| Range | 50-100 | 60-100 | 50-100 |
| Tumor stage (n [%]) | | | |
| T1 | 121 (64.0) | 30 (61.2) | 91 (65.0) |
| T2 | 32 (16.9) | 9 (18.3) | 23 (16.4) |
| Metastasis | 25 (13.2) | 7 (14.3) | 18 (12.9) |
| Multifocal | 15 (7.9) | 5 (10.2) | 10 (7.1) |
| Dosimetry | | | |
| Dose per fraction (Gy/fraction) (n [%]) | | | |
| 10 | 166 (87.8) | 43 (87.8) | 123 (87.9) |
| 12 | 23 (12.2) | 6 (12.2) | 17 (12.1) |
| Mean V20 | 5.65 | 6.42 | 5.42 |
| Mean lung dose | 382 | 424 | 372 |
| Tumor location (n [%]) | | | |
| Upper lobes | 116 (61.4) | 31 (63.3) | 85 (60.7) |
| Lower lobes | 62 (32.8) | 13 (26.5) | 49 (35.0) |
| > 1 lobe | 11 (5.8) | 5 (10.2) | 6 (4.3) |
| Incidental concurrent medications (n [%]) | | | |
| ACE inhibitors | 49 (26) | | |
| ACE inhibitor subclass (n [%])* | | | |
| Lisinopril | 39 (80) | | |
| Enalapril | 4 (8) | | |
| Benzapril | 2 (4) | | |
| Ramipril | 2 (4) | | |
| Quinapril | 1 (2) | | |
| Trandolapril | 1 (2) | | |
| ARB | 22 (12) | | |
| Bronchodilator | 121 (64) | | |
| Aspirin | 68 (36) | | |
| Nitrates | 90 (48) | | |
| PDE-5 inhibitor | 5 (3) | | |
| ERA | 2 (1) | | |

*Percent of patients on subclass of ACEi compared with all ACEi users.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist; ERA, endothelin receptor antagonist; PDE-5, phosphodiesterase-5.

angiotensin receptor blockers, and patients on bronchodilators showed a trend toward increased risk for development of symptomatic pneumonitis. This may indicate that bronchodilator use is a marker for possibly worse underlying lung function predisposing patients to radiation toxicity. In addition, we did not demonstrate a difference in pneumonitis development based on tumor location in the lung (upper vs. lower/middle lobes), as has been previously demonstrated in setting of conventional fractionation.^{18,19}

Controversy remains whether pharmacologic manipulation of the renin-angiotensin system modulates development of pneumonitis after radiation therapy to the lung and the direct mechanism of action relating to ACEi radioprotection has not been elucidated. Initial reports relied on dependence of a thiol moiety in captopril supporting a radioprotective mechanism centered on neutralization of the oxidative stress precipitated by ionizing radiation, but preclinical studies have documented efficacy in classes of ACEi other than captopril and those not containing thiol.^{20,21} Our report demonstrated a protective effect with noncaptopril ACEi users, as the majority of patients were incidentally prescribed the ACEi lisinopril. Attenuation

TABLE 3. Development of Radiation Pneumonitis by Subclass of Medications Concurrently on During SBRT

| | No Clinical Radiation Pneumonitis (n = 167) | Clinical Radiation Pneumonitis (n = 25) | |
|----------------|---|---|-------|
| ACE inhibitors | | | 0.03* |
| No | 117 (71%) | 23 (92%) | |
| Yes | 47 (29%) | 2 (8.0%) | |
| ARB | | | 0.50† |
| No | 146 (89%) | 21 (84%) | |
| Yes | 18 (11%) | 4 (16%) | |
| ASA | | | 0.18* |
| No | 102 (62%) | 19 (76%) | |
| Yes | 62 (38%) | 6 (24%) | |
| Nitrates | | | 0.99† |
| No | 156 (95%) | 24 (96%) | |
| Yes | 8 (4.9%) | 1 (4.0%) | |
| ERA | | | 0.25† |
| No | 163 (99%) | 24 (96%) | |
| Yes | 1 (0.6%) | 1 (4.0%) | |
| PDE-5 | | | 0.51† |
| No | 160 (98%) | 24 (96%) | |
| Yes | 4 (2.4%) | 1 (4.0%) | |
| Bronchodilator | | | 0.07* |
| No | 63 (38%) | 5 (20%) | |
| Yes | 101 (62%) | 20 (80%) | |

*Pearson χ^2 test of association.

†Fisher exact test.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ASA, acetyl salicylic acid; ERA, endothelin receptor antagonist; PDE-5, phosphodiesterase-5.

of radiation-induced changes in pulmonary vascular hemodynamics and/or inhibition of angiotensin II mitigated pulmonary collagen synthesis leading to pulmonary fibrosis have also been explored as possible mechanisms.^{6,8}

Four previous clinical reports in the literature have retrospectively reviewed the concurrent use of ACEi and effects on radiation-induced lung toxicity in the setting of conventionally fractionated external beam radiation therapy.⁹⁻¹² An earlier report found no difference in the development of pneumonitis in patients prescribed concurrent ACEi while

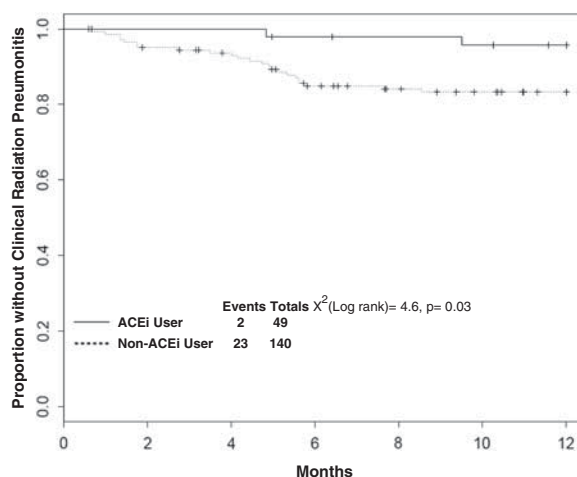
**FIGURE 1.** Time to development of symptomatic radiation pneumonitis in ACEi users vs. nonusers.

TABLE 4. Univariate Analysis of Clinicopathologic Characteristics and Treatment Dosimetric Endpoints

| | Grade <2 Pneumonitis (N = 164) | Grade 2 + Pneumonitis (N = 25) | P |
|------------------------------------|--------------------------------------|--------------------------------------|--------|
| Mean age (SD) | 71.18 (10.37) | 70.04 (9.77) | 0.61* |
| Sex | | | 0.04† |
| Female | 68 (42%) | 5 (20%) | |
| Male | 96 (59%) | 20 (80%) | |
| Median KPS (IQR) | 80 (70-90) | 80 (70-90) | 0.54‡ |
| Median dose (IQR) (Gy) | 50 (50-50) | 50 (50-50) | 0.88‡ |
| Median year (IQR) | 2010 (2009-2012) | 2011 (2009-2012) | 0.57‡ |
| Fractions | | | 0.008§ |
| 4 | 1 (0.6%) | 3 (12%) | |
| 5 | 163 (99%) | 22 (88%) | |
| Clinical stage | | | 0.43‡ |
| T1a | 81 (49%) | 10 (40%) | |
| T1b | 23 (14%) | 6 (24%) | |
| T2a | 16 (9.8%) | 2 (8.0%) | |
| T2b | 13 (7.9%) | 1 (4.0%) | |
| T3 | 5 (3.0%) | 0 | |
| T4 | 2 (1.2%) | 0 | |
| Metastasis | 21 (13%) | 4 (16%) | |
| Recurrence | 3 (1.8%) | 2 (8.0%) | |
| Lobe | | | 0.36§ |
| Upper | 102 (62%) | 14 (56%) | |
| Lower | 54 (33%) | 8 (32%) | |
| >1 isolation | 8 (4.9%) | 3 (12%) | |
| Median V20 Gy (IQR) (N) | 4.25 (2.40-7.50) (N = 118) | 5.13 (1.68-8.63) (N = 14) | 0.83‡ |
| Median V12.5 Gy (IQR) (N) | 7.80 (5.00-12.90) (N = 119) | 9.93 (3.94-16.23) (N = 14) | 0.99‡ |
| Median V5 Gy (IQR) (N) | 16.81 (12.30- 27.00) (N = 119) | 19.55 (10.79- 25.50) (N = 14) | 0.77‡ |
| Median MLD (IQR) (cGy) | 314 (200-493) (N = 59) | 435 (221-640) (N = 9) | 0.44‡ |
| Pretreatment pulmonary fibrosis | | | 0.58§ |
| Present | 5 (3%) | 1 (4%) | |
| Not present | 159 (97%) | 24 (96%) | |

*Independent samples *t* test with equal variances assumed.†Pearson χ^2 test of association.

‡Wilcoxon rank-sum test.

§Fisher exact test.

IQR indicates interquartile range; KPS, Karnofsky performance status.

TABLE 5. Effect on Developing Grade 2+ Pneumonitis After Controlling for All Other Variables in the Multivariate Model

| | OR (95% CI) | P |
|-----------------------------|---------------------|------|
| Sex | | |
| Male vs. female | 2.27 (0.78-6.65) | 0.14 |
| Fractions | | |
| 4 fractions vs. 5 fractions | 17.82 (1.44-220.54) | 0.02 |
| ACE inhibitor | | |
| Yes vs. no | 0.17 (0.03-0.89) | 0.04 |
| ASA | | |
| Yes vs. no | 0.49 (0.17-1.40) | 0.18 |
| Bronchodilator | | |
| Yes vs. no | 3.17 (1.03-9.74) | 0.04 |

Significance determined using penalized binary Firth logistic regression.

ACE indicates angiotensin-converting enzyme; ASA, acetyl salicylic acid; CI, confidence interval; OR, odds ratio.

greater freedom from grade ≥ 2 RP, after controlling for confounders in multivariate analysis. Our dataset independently supports these conclusions.

Limitations of this study are centered on the retrospective design, exposing to the possibility of selection bias and confounders. Medication compliance may also have varied between patients. Significant interobserver variability in lung toxicity grading may also exist, making lung toxicity grading especially difficult in the setting of the expected deteriorating lung function in the patient population receiving lung SBRT. Encouragingly, our rate of symptomatic pneumonitis of 13% closely matches that of previous lung series.²²⁻²⁴ In addition, multivariate analysis addressing identified possible cofounders continued to show decreased risk of pneumonitis in ACEi users.

With the advent of increased lung cancer screening as well as expanding role for treating synchronous, metachronous, or oligometastatic disease, identifying toxicity modifiers in this population with often compromised lung function is important.^{25,26} In addition, several questions still remain about the timing and use of ACEi, whether concurrent use or continued use after SBRT is important, as well as whether the subclass of ACEi and dose is important in modulating the protective effect.

We demonstrated in our cohort of patients an independent effect from ACEi use and decreased rates of clinical pneumonitis toxicity. ACEi may represent an important toxicity modifier that warrants further clinical trial investigation.

CONCLUSIONS

Incidental concurrent use of ACEi demonstrated efficacy in diminishing rates of symptomatic pneumonitis in the setting of lung SBRT after correcting for clinicopathologic and treatment characteristics. Prospective analysis is needed to confirm these findings.

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