Renin-Angiotensin System Inhibitors Might Help to Reduce the Development of Symptomatic Radiation Pneumonitis After Stereotactic Body Radiotherapy for Lung Cancer

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Abstract

The use of a renin-angiotensin system (RAS) inhibitor might prevent the occurrence of symptomatic radiation pneumonitis (RP) after radiotherapy for lung tumors. Stereotactic body radiotherapy (SBRT) is often delivered to patients not suitable for surgery; however, it might not be tolerated because most of these patients have advanced age and/or comorbidities. The use of a RAS inhibitor was associated with a reduced occurrence of grade ≥ 2 RP after SBRT for lung lesions.

Introduction: The purpose of the present study was to evaluate the role of renin-angiotensin system (RAS) inhibitors in preventing symptomatic radiation pneumonitis (RP) after stereotactic body radiotherapy (SBRT). **Materials and Methods:** The data from 158 patients with a solitary lung lesion treated with 1 to 3 fractions of SBRT from December 2008 to July 2014 were retrospectively analyzed. The incidence of RP was evaluated according to the Common Toxicity Criteria for Adverse Events, version 4. The use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) was analyzed to assess for possible correlations with the development of grade $\geq$ 2 RP. The patient and dosimetric variables were also assessed. **Results:** After a median follow-up period of 13.8 months (range, 3.2-55.0 months), 22 patients had developed grade $\geq$ 2 RP. Patients with peripheral lesions, favorable dosimetric data, and ACEI and/or ARB use had a reduced risk of symptomatic RP. In unadjusted and adjusted multivariate analyses, ACEI and/or ARB intake and the dosimetric variables were statistically significant factors. In a secondary analysis, the use of ACEIs and ARBs among patients with a greater planning target volume and higher dosimetric values correlated with a reduced risk of symptomatic RP. **Conclusion:** The use of a RAS inhibitor was associated with a decreased incidence of symptomatic RP among patients undergoing SBRT for lung lesions. Patients with higher dosimetric values had a reduced risk of grade $\geq$ 2 RP with ACEI and ARB use.

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Introduction

Stereotactic body radiotherapy (SBRT) is able to deliver a high radiation dose to the tumor, resulting in a local control rate of $\geq$ 90% when doses > 100 Gy of the biologic effective dose (BED10; α/β ratio = 10 Gy) are used.[1-3] Despite the premature closure of 3 randomized trails comparing surgery and SBRT (ie, the American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021 for high-risk operable patients, the radiosurgery or surgery for operable early stage non-small cell lung cancer - ROSEL trial, and the randomized study to compare CyberKnife to surgical resection in stage I non-small cell lung cancer -STARS trial), SBRT currently represents the treatment of choice for inoperable stage I non–small-cell lung cancer (NSCLC).[4-7] Because of the high local control rate achieved in early-stage NSCLC, SBRT also plays a role as effective treatment of lung metastases.[8,9]

The incidence of symptomatic radiation pneumonitis (RP) after SBRT is usually low, ranging from 9% to 28%.[3,10-13] The volumes

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treated are typically small, allowing the delivery of high radiation doses to the target volume, sparing the surrounding healthy tissue, reflected in the low rate of RP observed. However, SBRT might not be tolerated because most patients will have advanced age and/or comorbidities. To date, several dosimetric and clinical factors that might correlate with the development of RP have been described.[12-17]

Blockade of the renin-angiotensin system (RAS) might correlate with a potential reduction of pneumonia risk and/or mortality in several clinical circumstances.[18-21] Moreover, angiotensin-converting enzyme inhibitors (ACEIs) have been shown to reduce the risk of radiation-induced lung injury in preclinical models.[22-24] Recently, some studies of the concomitant use of ACEIs in patients affected by NSCLC undergoing definitive conformal radiotherapy (CRT) have been published. Three of these studies reported a decreased risk of RP with the concurrent use of ACEIs.[25-27] One study found that only male patients or patients with a mean lung dose (MLD) of < 20 Gy might receive some benefit from ACEI use.[28] In contrast, only limited data on angiotensin receptor blockers (ARBs) and the risk of radiation-induced pneumonia are available, although they could have a possible role in this setting.[22,29,30]

Currently, studies on the potential efficacy of ACEIs and/or ARBs in decreasing the risk of symptomatic RP after SBRT have not been reported. Therefore, the purpose of the present report was to evaluate whether the use of concurrent ACEIs and/or ARBs is associated with a reduction of symptomatic RP after SBRT in patients treated for inoperable early NSCLC or solitary lung metastases.

Materials and Methods

Patient Characteristics and Eligibility Criteria

All inoperable patients affected by histologically confirmed stage I or recurrent NSCLC or with lung metastases were considered eligible for SBRT. Lung metastases were diagnosed by the appearance of a new lesion on the computed tomography (CT) or fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scan during the follow-up period for the primary cancer. Patients were excluded if they had insufficient follow-up data (≤ 3 months), had received previous RT to the lungs (SBRT and/or CRT), had been treated for > 1 lesion, or had no dosimetric plans available. Before treatment, all patients underwent clinical assessment consisting of a complete history and physical examination and total body CT and/or FDG-PET scans.

The data were prospectively collected and retrospectively analyzed. The present study was performed in accordance with the Declaration of Helsinki, and all patients provided written informed consent.

Simulation and Treatment

The SBRT technique used has been previously described.[31] All patients underwent CT simulation using a stereotactic body frame. For all patients, a basal helical CT scan and a 10-phase 4-dimensional (4D)-CT scan in free breathing were obtained. The maximum intensity projection was reconstructed using commercial software (Advantage 4D; General Electric) from the 10-phase 4D-CT scan and was used to delineate the internal target volume (ITV). The planning target volume (PTV) originated from the ITV with the addition of a 4-mm margin in all directions. The planning CT scan was registered with pretreatment diagnostic studies, such as the CT scan with contrast medium and/or the FDG-PET scan, to better delineate the target. The organs at risk, such as the lungs, heart, spinal cord, bronchial tree, and esophagus, were contoured on the basal CT scan. A SBRT plan with the Eclipse planning system (Varian, Palo Alto, CA) was calculated using 7 to 9 coplanar and/or noncoplanar beams. Treatment was delivered with a 6-MV linear accelerator in 1 to 3 fractions. A daily kilovoltage cone beam CT scan was used to verify the position. Three radiation doses were considered: 23 Gy in 1 fraction or 15 Gy in 3 fractions for central lesions, depending on the tumor size or treating physician preference, and 30 Gy in 1 fraction for peripheral lesions. The doses were prescribed to 95% of the maximum dose. A tumor was considered central when situated within 2 cm of the proximal bronchial tree.[32]

The dose–volume constraints were as follows: spinal cord < 14 Gy (single fraction) and < 18 Gy (3 fractions); esophagus < 15.4 Gy (single fraction) and < 27 Gy (3 fractions); brachial plexus < 17.5 Gy (single fraction) and < 24 Gy (3 fractions); and heart < 22 Gy (single fraction) and < 30 Gy (3 fractions).

Outcome and Toxicities

All patients were prospectively followed up at 30 to 45 days from the end of treatment and every 3 months thereafter. At each visit, the patients underwent a physical examination and CT or FDG-PET. The occurrence of grade ≥ 2 RP was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4, in association with the corresponding radiologic abnormalities on the CT scan. Patients with clinical symptoms and without the CT appearance of pneumonitis were not considered to have RP. In accordance with the CTCAE, version 4, RP was graded as follows: grade 1, asymptomatic RP observed on diagnostic imaging and not requiring intervention; grade 2, symptomatic RP requiring medical intervention; grade 3, severe symptoms limiting patient self-care and requiring oxygen; grade 4, life-threatening respiratory compromise requiring urgent intervention; and grade 45, death from RP. For each patient, the clinical factors, including age, gender, smoking status, and concomitant medication, and dosimetric factors, including gross tumor volume (GTV), PTV, ipsilateral MLD, contralateral MLD, bilateral MLD, and the percentage of nontumorous lung receiving > 5, > 10, > 15, and > 20 Gy of RT (V_5, V_{10}, V_{15}, and V_{20}, respectively), were recorded. Because of the different fractionation schedules used, all the dosimetric variables were converted to the 2-Gy equivalent total dose using the linear quadratic model, with an α/β ratio of 3 Gy based on data from conventionally fractionated RT.[33]

Statistical Analysis

We performed a comparison of between-group clinical and dosimetric characteristics according to the use of ACEIs or ARBs, or both, using the χ^2 test or Mann-Whitney U test. The median follow-up point was analyzed using the reverse Kaplan-Meier method.[34] The Kaplan-Meier method was used to calculate the freedom from symptomatic (grade ≥ 2) RP (FFSRP). Univariate and multivariate analyses were performed using the Cox proportional hazard method. The Pearson correlation coefficient was used to assess the correlation among the dosimetric variables (ie, V_5, V_{10}, V_{15}, V_{20}, total MLD, ipsilateral MLD, and contralateral MLD). A secondary analysis using the Cox proportional hazard method was performed to evaluate the correlation of patient characteristics and