Prospective Exploratory Analysis of Cardiac Biomarkers and Electrocardiogram Abnormalities in Patients Receiving Thoracic Radiation Therapy with High-Dose Heart Exposure

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Introduction: Acute effects of incidental cardiac irradiation in patients treated for thoracic cancer are not well characterized. We evaluated longitudinal changes in cardiac biomarkers for patients undergoing conformal radiation therapy (RT) with thoracic malignancies with high-dose cardiac exposure.

Methods: Twenty-five patients enrolled in a prospective trial (February 2009–December 2012) received more than or equal to 45 Gy to the thorax, with pretreatment estimates of more than or equal to 20 Gy to the heart. Chemotherapy was allowed except for doxorubicin or fluorouracil. Electrocardiographic (ECG), troponin-I (TnI), and brain natriuretic peptide (BNP) measurements were obtained before RT, within 24 hours of the first fraction, at the end of RT, and at first follow-up (1–2 months). These biomarkers were quantified at specific times and changes from baseline were evaluated with paired *t* tests.

Results: The median heart dose was 25.9 Gy (range 10.1–35.1 Gy). After the first RT fraction, no changes were noted in ECG or median TnI or BNP levels; at the end of RT, two patients had elevated TnI and BNP, but neither difference was statistically significant. At first follow-up, TnI had returned to normal but the median BNP remained elevated ($p = 0.042$). BNP did not increase over time in the 18 patients who received only RT. Twelve patients experienced acute ECG changes during RT, which resolved in seven patients by the next measurement. No patients experienced clinically significant RT-related events.

Conclusion: Increases in BNP and ECG changes were observed during high doses of radiation to the heart. The findings of this pilot study warrant further investigation and validation.

Key Words: Cardiac toxicity, Radiation therapy, Lung cancer, Brain natriuretic peptide.

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Radiation therapy (RT) for cancer that involves the thorax sometimes involves unavoidable exposure of the heart to high radiation doses, even when advanced RT technologies are used. Although the long-term effects of low-dose cardiac exposure are relatively well known, the acute effects, if any, are not. Moreover, most prior studies have focused on the long-term effects of radiation among survivors of Hodgkin's lymphoma or patients receiving radiation for left-sided breast cancer, and most involved exposure of large portions of the heart to low radiation doses.[1–5] The conclusions from these studies cannot be extrapolated to patients being treated for thoracic malignancies such as lung cancer for several reasons. First, with the advent of increasingly conformal RT techniques, the dose distributions across the heart can differ substantially, with focal regions receiving high doses but other portions spared almost completely. Second, patients being treated for lung cancer often differ from those treated for breast cancer or Hodgkin's lymphoma in that they tend to be older and to have underlying cardiopulmonary conditions such as coronary artery disease or chronic obstructive pulmonary disease. For these reasons, heart exposure for patients being treated for thoracic malignancies, with modern techniques, should be studied separately from that for patients with other forms of cancer.

The purpose of this study was to prospectively evaluate biomarkers of cardiac function among patients receiving high-dose conformal RT for thoracic malignancies. Specifically, we quantified brain natriuretic peptide (BNP) and troponin-I (TnI) levels, and electrocardiographic (ECG) differences, before, during, and after RT, and we assessed whether cardiac dose was associated with changes in these values over time. We also documented clinical events to determine whether the occurrence of such events correlated with changes in these biomarkers.

PATIENTS AND METHODS

Patient Selection

This study was approved by the appropriate institutional review board at The University of Texas MD Anderson Cancer Center. Patients were enrolled from February 2009 to December 2012. Inclusion criteria were having (1) a primary

thoracic malignancy (lung cancer, esophageal cancer, thymoma, or malignant mesothelioma) and (2) an estimated mean cardiac dose of more than or equal to 20 Gy at treatment simulation (assessed by the treating physician). Our institution treats approximately 200 patients per year definitively for lung cancer, and as such the study was initially designed to include patients who received only RT. However, initially there were difficulties with enrollment because many patients who had a mean heart dose more than 20 Gy received chemotherapy or had other histologies (e.g., mesothelioma). At that point, in late 2011, the enrollment criteria were expanded to include patients with other histologies and patients treated with concurrent chemotherapy as long as the chemotherapy regimen did not include doxorubicin or fluorouracil owing to the potential cardiotoxicity of those drugs. Enrollment then increased substantially and the trial was closed in the next year. Exclusion criteria of the study were a recent (within 3 months) history of cardiac events (myocardial infarction, decompensated heart failure, or myocarditis/pericarditis) or renal failure (serum creatinine ≥2.0), or having a pulmonary embolus during the month before RT. Patients with a remote history of these events were not excluded because we sought to evaluate acute changes regardless of cardiac history.

Study Evaluations

All patients underwent a complete history and physical examination and ECG, BNP, and troponin level measurements before study entry. ECG measurements were obtained with 12-lead devices, and blood samples were drawn for BNP and TnI assessment after the first RT fraction, on the last day of radiation or chemoradiation, and at the first follow-up visit (1–2 months after completing RT). These measurement points were chosen to address the primary study aim, that is, determine whether high radiation doses led to acute changes in these cardiac biomarkers or ECG findings; a future aim was to determine whether such changes could be associated with subsequent long-term events.

Heart Contouring

For all patients, the heart was contoured by using a model-based segmentation method that was then adjusted manually to ensure that the entire structure was encompassed. For the purposes of treatment planning, the heart was defined superiorly as directly inferior to the aortic arch through the apex, and included both atria and ventricles. The pericardium was also encompassed within the heart contour.

Cardiac Biomarkers

For the cardiac biomarker analysis, we chose to assess TnI because it is a more sensitive measure of myocardial injury than is creatine kinase-myocardial band (CK-MB) or troponin T (TnT). We chose to assess BNP as an indicator of left ventricular function and congestive heart failure.

TnI levels were measured with the Unicel Dxl Access Immunoassay System (Beckman Coulter, Brea, CA), in which concentrations of the analyte are determined from a stored, multipoint calibration curve. The detection limit of this assay for TnI is 0.03 ng/ml (normal range 0–0.03 ng/ml, reportable range 0.03–100 ng/ml). BNP was measured by using the Triage Method with a Beckman Coulter UniCel Dxl 600 Access Immunoassay system (normal range 0–100 pg/ml; reportable range 1–5000 pg/ml). The sensitivity, specificity, and negative predictive value of troponin for myocardial infarction has been shown in previous studies to be 85% or higher, whereas the positive predictive value ranges from 65% to almost 90%.[6,7]

Blinded Analysis of Electrocardiograms

All ECGs were analyzed after acquisition by a cardiologist (W.Y.) in a blinded manner for the following characteristics: normal ECG, sinus tachycardia/bradycardia, conduction abnormalities (e.g., bundle branch block, atrial fibrillation), and ischemic changes. Subsequent ECGs were then analyzed to determine whether any acute changes had resolved.

Statistical Methods

Our primary objective was to investigate (1) the relationship between cardiac radiation dose and cardiac biomarker levels and (2) the temporal relationship between RT delivery and anticipated elevation of cardiac biomarkers. The distribution of BNP levels was reported as baseline (i.e., before RT) and change over time. Paired *t* tests were used to assess whether BNP levels changed over time, specifically if the change in mean levels was different than 0. Repeated measures regression analysis was then used to determine the effect of heart dose and time since baseline on BNP level. Ninety-five percent confidence intervals (CIs) were determined for the mean change in BNP from baseline to day 1 of RT, to the end of RT, and to the first follow-up visit. Repeated measures regression analysis was used to assess the time since baseline on BNP level and to identify any statistically significant increases in BNP level over time. We also included an interaction term for MHD and time in our model to allow for the possibility that the effect of MHD on change in BNP varied with time. Because of the repeated measures analysis, we had 40 degrees of freedom for testing the interaction term and the term for time, because patients contribute data at each time point. Finally, we used the Spearman correlation to determine the correlation between mean heart radiation dose and change in BNP, both at the end of RT and at the 1- to 2-month follow-up period. These analyses were then repeated for the 18 patients who received only RT to identify trends without the potential confounding effect of chemotherapy.

A Bonferroni correction was used in the sample-size justification based on tests of the correlation between radiation dose and the change from baseline at three different time points for all patients and for patients who received RT alone, for a total of six tests. With 25 patients, we had 80% power to detect a correlation of 0.60 or greater, with a one-sided significance level of 0.008.

RESULTS

Patient Characteristics

Characteristics of the 25 patients enrolled in this study are listed in Table 1. Most patients (72%) were male and had

