Evaluating Cardiac Biomarkers after Chemotherapy and Proton Therapy for Mediastinal Hodgkin Lymphoma

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Abstract

Purpose: Late cardiac complications from thoracic radiation of patients with Hodgkin lymphoma are of great concern. The authors investigated whether cardiac biomarkers could identify patients with early cardiac damage from thoracic radiation.

Materials and Methods: Following completion of anthracycline-based chemotherapy, 14 patients with stage I-IIIA mediastinal Hodgkin lymphoma were enrolled on an IRB-approved prospective trial and agreed to serum evaluation of troponin, CK-MB, and BNP before beginning radiation, after completing radiation, and every 3 to 6 months for 5 years, during follow-up or until relapse.

Results: Among the 14 patients, median follow-up for the entire cohort was 5 years. No evidence in abnormal values in troponin or CK-MB was observed among the patient cohort. BNP levels demonstrated statistically significant higher values at various follow-up time points. Higher levels of BNP were observed among patients receiving higher anthracycline doses (>250 mg), but not among patients with higher mean heart radiation doses.

Conclusions: In the first 5 years after treatment, no rise in CK-MB or troponin was identified. BNP levels significantly increased following treatment, with larger increases among patients who received higher doses of anthracyclines. Further investigation is warranted.

Keywords: Hodgkin lymphoma; radiation therapy; chemotherapy; cardiac biomarker

Introduction

Survivors of Hodgkin lymphoma (HL) who receive anthracycline-based chemotherapy and thoracic radiation are at high risk of developing late cardiac toxicity [1] decades after treatment. In fact, a survivor of HL with the same cardiac risk factors as an individual who does not receive cancer treatment has a much higher relative risk of cardiac morbidity [1]. Radiation exposure to the heart can induce pathological changes, including pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, coronary artery disease, and valvular disease [1]. The consequences of radiation therapy can be grave; therefore, there is a need to identify these patients early, when more interventions may be available to them to delay or possibly reverse the processes.

Investigators have begun evaluating for markers of early cardiac damage using radiographic imaging, such as nuclear perfusion scans, cardiac MRI, echocardiogram, and computed tomography angiography. Yet these tests can be expensive, making them difficult to study. Serum biomarkers of cardiac damage are currently used to diagnose...
myocardial ischemia (e.g., troponin and creatine kinase [CK-MB]) and congestive heart failure (CHF; e.g., B-type natriuretic peptide [BNP]) and represent a less-expensive alternative for potentially identifying cardiac damage. The present study investigated the impact of thoracic radiation on serum cardiac biomarkers during the first 5 years of follow-up.

**Patients and Methods**

Between June 2008 and 2012, 15 patients with stage I-IIIA HL enrolled in an institutional review board-approved prospective clinical study of proton therapy that included evaluation of serum cardiac markers. Cardiac markers were assessed following the completion of chemotherapy but prior to radiation for the baseline value. They were assessed every 3 months following completion of radiation for 2 years, and then every 6 to 12 months until 5 years following treatment or disease relapse. One pediatric patient (age 6 years) was excluded owing to the discomfort of multiple blood draws. The patient and treatment specific details of the remaining 14 patients are included in Table 1.

Statistics were performed using JMP software (SAS Institute, Cary, NC). The Mann-Whitney test assessed BNP difference when comparing two independent groups; the Wilcoxon signed rank test was used to assess paired differences in BNP levels after treatment relative to baseline.

**Results**

The median follow-up for the entire cohort was 5 years with no new cardiac events related to radiation. One 15-year-old girl with pre-existing arrhythmia required an expected cardiac ablation.

Among all blood samples, CK-MB and troponin were unremarkable with a value of 0 at all time points. Figure 1 demonstrates BNP levels over time for the cohort. The mean and median BNP was elevated at all follow-up time points; however, it was statistically significantly elevated at 6, 12, 24, 48, and 60 months (p<0.05). When BNP was evaluated according to baseline anthracycline dose of <250 versus >250 mg/m², greater increases in BNP were observed with higher anthracycline dose at 60 months (p=0.025) relative to baseline. No observed difference was appreciated in BNP levels at 60 months relative to baseline based on mean heart dose (p=0.46), mean left ventricle dose (p=0.88), or right ventricle dose (p=0.65) of <10 Gy versus >10 Gy.

**Discussion**

In the present study, the authors did not find significant changes in CK-MB or troponin levels during the first 5 years of follow-up in survivors of HL who received anthracycline-based chemotherapy and mediastinal proton therapy. However, the authors did observe a statistically significant increase in BNP at several different time points.
BNP is released by the ventricles in response to stretch, making it a marker for hemodynamic stress [2, 3]. It relaxes vascular smooth muscle and promotes NaCl excretion. BNP is an important biomarker in the diagnosis and management of heart failure, and can also be used to predict the risk of heart failure before symptoms develop [3]. While BNP has a short half-life, only 18 minutes, its stimulus, ventricular stretch, lasts much longer [3]. This is opposed to other biomarkers used to diagnose acute cardiac syndromes, such as cardiac troponins or CK-MB, which are only detectable for a few days. CK-MB levels return to normal limits within 72 hours of an acute myocardial infarction [4]. A rise in cardiac troponins will last 7 to 10 days [4]. Because it is less limited temporally, BNP may be a good biomarker of long-term stress.

Although the sample size limited the authors’ ability to do a more robust analysis, no obvious relationship was seen between mean heart dose (<10 Gy vs. ≥10 Gy) and BNP levels. Also, the present study did not apply a correction for multiple observations, which could have increased the likelihood of statistical significance by chance alone. Therefore the results should be interpreted cautiously. Other studies have evaluated the impact of thoracic radiation and cardiac morbidity. Mulrooney et al [5] demonstrated that mean heart dose >15 Gy was associated with pericardial disease, CHF, myocardial infarction, and valvular abnormalities. These cardiac effects were clinically evident 5 years after diagnosis, but subclinical evidence of disease can exist earlier [5]. A more recent report demonstrated an increased risk of congestive heart failure with increasing radiation doses. Since CHF typically accompanied by elevated BNP, it is possible that a relationship between BNP levels and cardiac dose could become evident with longer follow-up.

Palumbo et al [6] looked at BNP as a marker of radiotherapy-related damage in left-sided breast cancer patients. They found that BNP increased transiently 6 months after treatment, and decreased 1 year after treatment, but remained above baseline levels [6]. This fluctuation matches the results in the present study. Palumbo et al [6] found significant correlation between radiation dose to the heart and normalized BNP levels (a ratio compared to baseline BNP) up to 1 year after treatment, but no correlations with absolute BNP levels. They also did not find any change in the left ventricle ejection fraction; therefore, any changes in BNP are subclinical and may predict damage [6].

On the other hand, despite small patient numbers, a trend for higher BNP levels was observed among patients who received a higher anthracycline dose (>250 mg). Mulrooney et al [5] demonstrated an increased risk of CHF (hazard ratio [HR], 5.2), pericardial disease (HR, 1.8), and valvular disease (HR, 2.3) with anthracycline doses >250 mg. They also found a significant increase in the risk of CHF in patients who received an anthracycline dose <250 mg (HR, 2.4), which is roughly equivalent to the increased risk of CHF in patients receiving an average cardiac radiation dose of 15 to <35 Gy (HR, 2.2) [5].

Investigators of 2 other studies analyzed the effects of anthracycline therapy on cardiac biomarkers and left ventricular stress, enrolling patients at least 2 and 5 years out of treatment [7, 8]. Armenian et al found that only NT-proBNP (not BNP or troponin T) levels correlated with left ventricular end-systolic wall stress, and that this was only true of survivors treated with >300 mg/m² of anthracyclines [7]. Mavinkurve-Groothuis et al found that roughly one-third of survivors treated with >300 mg/m² of anthracyclines had abnormal BNP levels, but this was not significantly related to reduced ejection fraction [8]. More mature data with longer follow-up is needed to observe if these early elevations in BNP translate to clinically meaningful heart complications decades later.
Conclusion
Cardiac troponin and CK-MB were not useful biomarkers at our follow-up time points. BNP, however, was elevated at several follow-up time points, which might be an early indicator of cardiac damage from either anthracyclines or radiation. Further investigation is warranted.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest Statement: Drs. Nancy P. Mendenhall and Bradford S. Hoppe are part of the International Journal of Particle Therapy’s editorial board.

Acknowledgments: The authors would like to acknowledge Keri Hopper, RN, for providing patient care and coordinating blood draws; Amanda Prince RS, BSN, CCRP, and Amanda Williams, BA, CCRP, for their work on coordinating the HL01; and Jessica Kirwan, MA, and Judy Tran for their editorial assistance. Lidia Guzhva was funded with the Goodman Research Award.

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