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Original Article

MEDiastinal Irradiation and CArdio-Toxic Effects (MEDICATE): Exploring the Relationship between Cardiac Irradiation and High Sensitivity Troponins

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Abstract

Aims: Radiation-induced heart disease is a late effect of cardiac irradiation and has been shown in patients with lymphoma and thoracic cancers. There is no established measurement tool to detect acute cardiac damage. However, high sensitivity troponin I and T (HsTnI and HsTnT) and echocardiograms have shown promise in some studies. A pilot trial was conducted to characterise whether these instruments may detect subclinical radiotherapy-induced cardiac damage.
Materials and methods: Eligible patients received high cardiac doses defined by either at least 30 Gy to 5% of cardiac volume or a mean dose of 4 Gy. HsTnI and HsTnT were measured before radiotherapy and after 2 and 4 weeks of radiotherapy; three-dimensional echocardiograms were completed before and 1 year after radiotherapy.
Results: Of 19 patients, the median 'mean left ventricular dose' was 3.1 Gy and the 'mean cardiac dose' was 8.6 Gy. Significant positive associations between HsTnI and HsTnT were observed at all time points, but there was no significant association with cardiac dose. The mean left ventricular dose and the maximum left ventricular dose were, however, associated with a decrease in ejection fraction ($P = 0.054, 0.043$) as well as an increase in left ventricular strain ($P = 0.058$).
Conclusion: This study suggests that HsTnI and HsTnT are intimately related, but detection of acute cardiac damage was not shown, potentially due to limitations of these markers or low radiotherapy doses using conformal techniques. Our results also suggest subacute damage at 1 year may depend on the dose to the left ventricle. Further studies are needed, as identification of early damage could facilitate the ability to closely monitor and intervene in patients at risk for radiation-induced heart disease.

Key words: Cardiac disease; cardiotoxicity; lymphoma; radiotherapy; troponin

Introduction

Radiation-induced heart disease is reported as a potential late adverse effect that typically develops several years after cardiac irradiation. Cardiac complications have been well-documented as a leading cause of non-cancer deaths in Hodgkin and non-Hodgkin lymphoma patients due to

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cardiotoxic treatments in combination with a favourable long-term prognosis [1]. In patients with mediastinal involvement, the proximity of disease to the heart can result in large cardiac volumes receiving high radiotherapy doses, even despite modern advances in cardiac protection techniques and reduced target volumes [2,3]. In addition, these patients receive pre-treatment with anthracycline (doxorubicin) chemotherapy, which has a reported cumulative dose-dependent risk of dilated cardiomyopathy of 1–5% at standard dosing (<550 mg/m^2) [4]. Given the young age, favourable prognosis and long-term survival in many lymphoma patients, the potential to develop chronic cardiac deterioration is a serious concern.

The deleterious effect of cardiac toxicity on survival has also been shown in other cancers of the thorax, emphasising the importance of early (subclinical) identification of acute and chronic cardiac toxicity [5–9]. In particular, Darby *et al.* [5] reported a significant linear increase in ischaemic events with radiotherapy dose in breast cancer patients beginning at threshold doses as low as 2 Gy. A recent SEER analysis showed that small cell lung cancer patients receiving radiotherapy, a group not previously considered to have a high cardiotoxicity risk, have a 5% absolute increase in cardiac events at 5 years [6]. Other studies have also shown that in patients with oesophageal and non-small cell lung cancer, despite a limited prognosis, the risk of cardiac events has been demonstrated to increase less than 2 years after radiotherapy [7,8]. The Radiation Therapy Oncology Group (RTOG) 0617 dose-escalation trial in non-small cell lung cancer reported worse overall survival in those patients in the high-dose arm (74 Gy versus 60 Gy), which correlated with the cardiac volume receiving 5 Gy and 30 Gy [9].

Yet, although the overall risk of cardiac toxicity and increased risk of cardiac death has been well documented, the contribution of radiotherapy to acute cardiac muscle damage in patients receiving combined-modality treatments is less well defined. In the era of minimising radiotherapy dose and field size, this is particularly true [10]. This may in part be due to the fact that an early measure to reliably predict cardiac damage has not yet been established. Imaging modalities, including echocardiograms [11], and serum biomarkers, including C-reactive protein (CRP) and high sensitivity troponin I (HsTnI), have been suggested as predictors of cardiac risk [12]. However, studies testing their potential to detect acute cancer therapy-related damage have shown conflicting results [11,13–16].

A pilot study was conducted to investigate whether acute subclinical cardiac damage could be detected during a radiotherapy course using conformal practice protocols and planning techniques. Whereas other subclinical measurement tools have historically provided variable results, the recent use of high sensitivity troponins and nuclear imaging studies have been more promising. This study hypothesised that high sensitivity troponin T (HsTnT) and HsTnI elevations would be witnessed in the subacute period after cardiac radiotherapy with current conformal techniques and that left ventricular ejection fraction (LVEF) changes would be observed at 1 year on echocardiogram compared with baseline values. These tests could potentially assist in the identification and development of moderating therapies, radioprotective drugs and appropriate cardiac follow-up and intervention strategies after mediastinal radiotherapy.

Materials and Methods

Eligibility

A prospective single-institution pilot study of patients receiving high-dose or high-volume thoracic radiotherapy was conducted. The study was approved by the Hamilton Integrated Research Ethics Board. Patients were deemed eligible if over age 18 years, with a biopsy-proven malignancy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and a radiotherapy target volume located within or adjacent to the mediastinum, such that either 5% of the cardiac volume received 30 Gy or the heart received a mean dose of 4 Gy, regardless of disease histology. These dose and volume parameters were chosen based on previous studies [5,9]. Patients may have had chemotherapy or surgery before radiotherapy, but were not permitted to have concurrent systemic therapy during radiotherapy. At baseline risk documentation, smoking status was included if greater than 10 pack years and having quit within 5 years, as well as details of known cardiac risk factors (myocardial infarction or other ischaemic cardiac disease or cardiomyopathy).

Radiotherapy and Follow-up

Once the decision to treat was made, patients provided written informed consent to participate in the study and radiotherapy planning computed tomography scans were obtained. The cardiac organ at risk volumes (including the ventricles and the whole heart) were outlined per the Feng *et al.* [17] cardiac atlas. Radiotherapy planning was completed at the discretion of the radiation oncologist according to standard disease site guidelines and organ at risk tolerances. Charts were reviewed until the patient's last visit for any cardiac events that occurred following treatment (1 year), defined as myocardial infarction, congestive heart failure, requirement of cardiac procedure or cardiac death.

Blood Collection

HsTnI and HsTnT were chosen based on their utility in detecting acute cardiac damage during treatment in other systemic therapy and radiotherapy studies [18–21]. Patients had blood samples drawn prior to and after 2 and 4 weeks of radiotherapy. These measurement points were chosen based on the results of previous studies [18–20]. Blood samples were aliquoted and frozen in an institutional centralised clinical trials laboratory for the remainder of the study. At study completion, samples were run for each time point. Quantitative testing was completed using the Roche Modular Analytics Systemic (P800 instrument) immunoturbidimetric

assay for CRP and electrochemiluminescent immunoassay for HsTnT. The Architect i1000SR automated analyser was used for quantitative two-step chemiluminescent microparticle immunoassay quantitative testing for HsTnI. The testing ranges for CRP, HsTnT and HsTnI were 0.3–350 mg/l, 3–10 000 ng/l and 1–50 000 ng/l, respectively. Expected values for healthy subjects for CRP, HsTnT and HsTnI were <5 mg/l, 14 ng/l (99th percentile) and 26.2 ng/l (99th percentile), respectively.

Imaging

Three-dimensional echocardiograms were completed before the start of radiotherapy and at 1 year (subacutely) following radiation. The LVEF and global longitudinal left ventricular strain (LVS) were assessed by two cardiologists (DL, HD), with an expertise in the interpretation of three-dimensional echocardiograms.

Statistical Analysis

Contoured radiotherapy plans were reviewed to determine the maximum dose, mean dose and dose to a maximum 5% of the volume of the whole heart and left ventricle. Summary statistics were used to describe respondent characteristics and responses. The changes in marker values (HsTnI, HsTnT, CRP, LVEF and LVS) over time were calculated as an absolute value and assessed in relation to each other and to cardiac and left ventricular dose parameters, with a positive value indicating an increase in marker over time. The association between marker values was calculated using the Spearman rank correlation coefficients. For simplicity, correlation coefficients between +0.30 and −0.30 are assumed to have minimal or no statistical association, whereas correlation coefficients >|0.60| are considered to be moderate to large. One-sample *t*-tests were carried out to investigate whether marker values significantly changed over time from baseline. Tests were two-sided and a *P*-value of 0.05 or less was considered statistically significant and no adjustment for multiple testing was carried out. Note that as this was a small pilot study with multiple tests performed, appropriate caution is needed not to over-interpret the significance of any *P*-values. A sample size of 20 patients has >80% power to detect associations (two-sided, $\alpha = 0.05$), which are at least moderately large ($\rho = 0.60$) in size.

Results

In total, 24 patients were approached and 20 agreed to participate between December 2014 and August 2016. Nineteen of the 20 patients contributed to the data analysis (one patient withdrew consent for personal reasons before data collection). None of the included patients had pre-existing cardiac disease or diabetes. Patient and disease characteristics, as well as radiotherapy treatment details, are summarised in Table 1. No patients experienced a cardiac event during clinical follow-up (median 7 months, range 6–23 months). Two patients had a diagnosis of thymoma and did not receive chemotherapy, but did undergo surgical resection before radiotherapy. The remaining 17 patients received anthracycline chemotherapy, which was completed about 1 month before radiotherapy.

All patients had radiotherapy volumes that met initial eligibility. Most patients were prescribed between 30 and

Table 1
Patient and treatment characteristics

Patient characteristics	
Gender	Number (%)
Male	12 (63.2)
Female	7 (36.8)
Median age	41 Range (24–79)
Smoking status	Number (%)
Smoker (>10 years)	1 (5.3)
Non-smoker (none to <10 years)	18 (94.7)
Cardiac history	Number (%)
Yes	0
No	19 (100)
Diagnosis	Number (%)
Hodgkin lymphoma	5 (26.3)
Non-Hodgkin lymphoma	11 (57.9)
Thymoma	2 (10.5)
Acute lymphocytic leukaemia	1 (5.3)
Chemotherapy	Number (%)
CHOP-R or CHOP	10 (52.7)
ABVD	5 (26.3)
Other	2 (10.5)
None	2 (10.5)
Number of anthracycline chemotherapy cycles (in patients receiving chemotherapy $n = 17$)	Number (%)
≤2	3 (15.8)
4	3 (15.8)
6	10 (52.6)
8	3 (15.8)
Cardiac dose group	Number (%)
Patients receiving at least 30 Gy to 5% of heart	13 (68.4)
Patients receiving less than 30 Gy to 5% of heart	6 (31.6)
Radiotherapy plan	Median (range)
Median prescription dose (Gy)	35.0 (12.0–50.0)
Number of fractions	17 (12–25)
Fraction size	1.9 (1.8–2.0)
Radiotherapy technique	Number (%)
IMRT or VMAT	4 (21)
Conventional (two field)	15 (79)
Whole heart	Median (range)
Median average dose (Gy)	8.6 (1–25.0)
Maximum dose to 5% of heart volume (Gy)	32.7 (1.4–48.0)
Left ventricle	
Mean dose	3.1 (0.5–26.1)
Maximum dose to 5% of left ventricular volume	13.2 (0.1–43.0)

IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated radiotherapy.
CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, CHOP-R = cyclophosphamide, doxorubicin, vincristine, prednisone, rituxan.

35 Gy, with a median of 17 fractions. All patients were treated with standard fractionation (1.8–2 Gy per fraction). The median value for 'mean left ventricular dose' was 3.1 Gy; the median value for 'mean total cardiac dose' was 8.6 Gy. The maximum cardiac dose (to the top 5% volume) was less than 30 Gy in six cases and more than 30 Gy in 13 cases.

Seven patients missed one biomarker time point due to non-compliance. The median values for CRP remained below threshold at 1.85, 2.15 and 2.4 mg/l at baseline, 2 and 4 weeks, respectively. The median values for HsTnI were 9.5, 9 and 7 ng/l and for HsTnT were 10.9, 14.2 and 12.05 ng/l, respectively, at baseline, 2 and 4 weeks into radiotherapy. Absolute values of HsTnI and HsTnT reached values above threshold (14 and 26 ng/dl, respectively) in four patients and both markers decreased in absolute value through the treatment course in each of these patients. There was no statistically significant change observed in CRP, HsTnI nor HsTnT from baseline to week 2 ($P = 0.36$, 0.80, 0.82 for each marker, respectively) or week 4 ($P = 0.97$, 0.21, 0.17). There was a positive association between HsTnI increase between weeks 2 and 4 and maximum cardiac left ventricular dose ($\rho = 0.66$, $P = 0.027$), but no other associations between serum markers and cardiac doses were observed.

An analysis of associations between CRP, HsTnI and HsTnT is presented in Table 2. There were statistically significant positive associations between HsTnI and HsTnT at all time points, with an apparent decrease in mean value. There were no associations seen between HsTnI or HsTnT and CRP levels. A scatter plot of HsTnI and HsTNT values over time is displayed in Figure 1.

All evaluable patients completed echocardiograms as per protocol. Ten patients (50%) had a decrease in LVEF at 1 year compared with pre-radiotherapy; however, this result was not statistically significant ($P = 0.6$). The prognostic effect of radiation on the change in echocardiogram findings is presented in Table 3. Although overall the mean change in LVEF for the whole cohort was non-significant (57.57% pre-radiotherapy and 56.4% post-radiotherapy), the mean dose to the left ventricle was associated with a decrease in ejection fraction from before radiotherapy to 1 year echocardiograms ($\rho = -0.46$, $P = 0.054$). The median

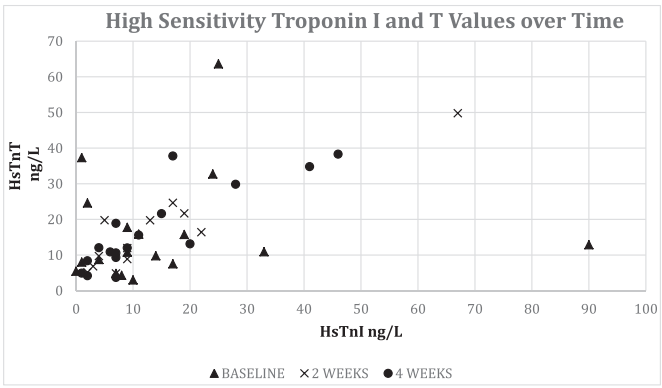

Fig 1. Scatter plot of high sensitivity troponin I (HsTnI) versus high sensitivity troponin T (HsTnT) values over time.

LVS before radiotherapy was 17.6 and after radiotherapy was 17.3 for the group. An association was seen between a decrease in LVS and mean left ventricular dose ($\rho = 0.46$, $P = 0.058$) and dose to the maximum 5% of left ventricular volume ($\rho = 0.48$, $P = 0.043$). There were no associations between changes in biomarkers and echocardiogram overtime.

Discussion

Cardiac damage is a well-recognised potential adverse effect of thoracic radiotherapy, which may cause significant morbidity and mortality, particularly in those patients with an otherwise favourable prognosis [1,2,5–9]. Early identification of cardiac damage could potentially facilitate tailored monitoring and interventions in these patients, but there is currently no established method to detect an increased risk of radiation-induced heart disease in the acute setting.

This study attempted to further characterise the utility of serum biomarkers and use of three-dimensional echocardiograms to detect subclinical radiotherapy-induced cardiac damage. In this patient population receiving mediastinal radiotherapy, troponins increased in only four patients, but without statistical significance. Measurements

Table 2
Serum biomarker associations

	High sensitivity troponin I (HsTnI)	High sensitivity troponin T (HsTnT)
Change from pre-radiation to week 2		
CRP	−0.53 ($P = 0.097$)	−0.35 ($P = 0.28$)
HsTnI		0.93 ($P \leq 0.001$)
Change from pre-radiation to week 4		
CRP	−0.52 ($P = 0.046$)	−0.40 ($P = 0.14$)
HsTnI		0.70 ($P = 0.004$)
Change from week 2 to week 4		
CRP	0.29 ($P = 0.36$)	0.37 (0.24)
HsTnI		0.78 (0.003)

CRP, C-reactive protein.

Table 3
Association between three-dimensional echocardiogram results and cardiac radiotherapy dose

Cardiac parameter	Spearman ρ	*P*-value
Outcome = change in ejection fraction, pre-radiation to 1 year post-radiation		
Maximum dose to whole heart	0.10	0.69
Mean dose to whole heart	−0.17	0.50
Dose to maximum 5% of heart	0.19	0.43
Mean left ventricular dose	−0.46	0.054
Maximum left ventricular dose	−0.35	0.16
Dose to maximum 5% of left ventricle	−0.36	0.14
Outcome = change in left ventricular strain, pre-radiation to 1 year post-radiation		
Maximum dose to whole heart	−0.09	0.71
Mean dose to whole heart	0.36	0.13
Dose to maximum 5% of heart	−0.11	0.67
Mean left ventricular dose	0.46	0.058
Maximum left ventricular dose	0.39	0.11
Dose to maximum 5% of left ventricle	0.48	0.043

of HsTnI and HsTnT remained associated with one another throughout the treatment course, suggesting that an association probably exists between cardiac troponins in intra-patient measurements, independent of systemic inflammation. Furthermore, there was a potential positive correlation between an HsTnI increase from weeks 2–4 and high mean cardiac doses ($P = 0.027$). However, it is difficult to know whether this finding is due to chance in this small population. As shown in Figure 1, there is no clear direction of change in overall values in the group over time.

HsTnI and HsTnT markers were chosen as a means of cardiac damage measurement based on their promising results in other studies. Dhesy-Thind *et al.* [18] identified a statistically significant increase in HsTnI between days 1 and 2 (mean of 15 versus 18, respectively) during trastuzamab immunotherapy in patients who had previously received anthracycline-containing chemotherapy. Other highly sensitive or ultrasensitive HsTnI assays have also been used to detect subclinical cardiac toxicity in radiotherapy patients. Raciki *et al.* [19] found a statistically significant elevation in ultrasensitive troponin I at 5 weeks into thoracic radiotherapy, as well as a significant correlation between ultrasensitive troponin I and D50 (dose to 50% of the heart). However, this study included a heterogeneous group of disease aetiologies among its patients and data analysis methods were not explicit. Skytta *et al.* [20] found that 21% of 58 left-sided breast cancer patients receiving radiotherapy had an increase in HsTnT levels. They also reported that the group of patients with a 30% increase in HsTnT values had statistically higher whole cardiac and left ventricular radiotherapy doses [20]. On the contrary, Gomez *et al.* [21] found no statistically significant elevations in troponin I during or after radiotherapy in patients receiving thoracic radiotherapy with high mean cardiac doses (median 25.9 Gy) and Serrano *et al.* [22] found no elevation in a panel of three cardiac markers (troponin I, N-terminal pro-brain natriuretic peptide, galectin 3) during or after radiotherapy. Therefore, although some studies have suggested that biomarker findings correlate with radiotherapy-mediated cardiac damage, consistency is lacking and the clinical utility of these findings has yet to be determined.

Whether acute cardiac inflammation is negligible during radiotherapy or simply not detected by the markers in this study is unknown. The mean dose to the heart and to the left ventricle (<4 Gy) in many of these patients was quite low, potentially due to improved shielding and techniques reducing cardiac dose. This may have precluded the detection of marker changes. Alternatively, troponin rise may have been measured too early in the course of radiotherapy and may have greater utility in the period after radiotherapy (>5 weeks).

Studies have also suggested that cardiac imaging modalities may play a role in identifying subacute cardiac damage [23]. It is not clear how much the total muscle volume contributes to acute damage as compared with vascular structures and which of the cardiac chambers are more sensitive to radiation effects [23]. Of all the biomarker and imaging tests completed in our study, significant associations all involved dose to the left ventricle. This is particularly important, as not only do the ventricles contain the bulk of the cardiac muscle, but dose escalation in the ventricles has been suggested as one of the most critical factors in the development of later cardiac toxicity [23–25].

Although the mean LVEF in this study did not change between pre-radiotherapy measurements and 1-year measurements, there were decreases observed in about half the patients ($P = 0.6$). A relationship may exist, however, between those with decreased LVEF and those receiving the highest left ventricular doses. An association was observed between decreased LVEF and mean dose to the left ventricle and between LVS and both left ventricular mean dose ($\rho = 0.46$, $P = 0.058$) and left ventricular dose to a maximum 5% volume ($\rho = 0.48$, $P = 0.043$). These results suggest that there may be functional changes induced by radiotherapy subacutely. The authors acknowledge, however, that a number of associations were tested and, therefore, these results must be interpreted with caution. Further studies must be conducted to characterise and confirm these findings.

Although valuable findings emerged in both serum marker testing and three-dimensional echocardiogram imaging, there are clear limitations to this study, which preclude more definitive conclusions. It was designed as an exploratory pilot trial and a small and somewhat heterogeneous patient population was included. Moderate mean cardiac and left ventricular doses were also observed in this cohort. In comparison, other studies documenting cardiac toxicity have included patients receiving significantly higher cardiac doses than the patients in this study [5,9]. This may be related to higher prescribed doses or different positioning of tumours in relation to the heart (e.g. lung or breast cancer). Although this may suggest that radiotherapy doses and techniques currently used in the treatment of mediastinal lymphoma (which compromised most of this cohort) may not induce enough cardiac damage to detect changes in these serum markers, definitive conclusions cannot be made based only on the study results. The

patients in this study were also a young age group (median 41 years), which is characteristic of lymphoma, and age may play a role in biomarker response to cardiac radiotherapy. For each of these reasons the results should be interpreted with caution. Further studies could focus primarily on those patients with lung or oesophageal cancer who may receive higher cardiac radiotherapy doses and represent a different age and risk demographic.

Second, the influence of anthracycline chemotherapy on baseline cardiac troponins cannot be delineated from this study. Absolute values of HsTnI and HsTnT may have been elevated by chemotherapy and therefore appeared to decrease again over time during radiotherapy. Recruiting patients prior to chemotherapy proved challenging due to the need for urgent treatment and variable referral patterns and further studies would be worthwhile to investigate the magnitude of effect of anthracycline therapy in these patients before radiotherapy.

Finally, although it was useful to obtain data on troponin levels at baseline and at 2 and 4 weeks, it is important to acknowledge that biomarker elevations may actually occur in the time period after radiotherapy (weeks to months). The time points of 2 and 4 weeks were chosen to measure acute elevations in these markers, based on findings in previous studies [17–21]. However, delayed measurements may have utility in detecting subacute elevations. Similarly, there is no standard or optimal process with respect to echocardiographic follow-up; evaluating echocardiograms immediately after radiotherapy and at more frequent intervals up to a year may have resulted in more significant findings.

Conclusion

Radiation-induced heart disease remains a primary concern following cardiac radiotherapy for Hodgkin lymphoma, non-Hodgkin lymphoma and other thoracic cancers, particularly in those patients receiving cardiotoxic chemotherapy. The results of this study suggest that HsTnI and HsTnT are intimately related, but detection of acute cardiac damage was not seen, potentially due to limitations of these markers or low radiotherapy doses using modern conformal techniques. However, the current study is reassuring; modern quality-assured radiation techniques may limit the extent of acute cardiac damage, even after anthracycline chemotherapy. These results also suggest that three-dimensional echocardiogram findings may be useful in detecting subacute damage at 1 year depending on the dose to left ventricular volumes. However, given the nature of this small pilot study, results must be interpreted with caution.

Ideally, early diagnosis of cardiac damage would help to moderate therapies and select patients for more intensive cardiac follow-up and intervention. As radiation-induced heart disease may manifest in a comparable manner to non-radiation-induced cardiac disease, it may likewise be managed in a similar manner if identified early. Detecting damage at an early stage could provide the ability to modify treatments, monitor patients closely in follow-up and intervene with cardioprotective agents. Larger scale studies will play an important role in defining the role of serum biomarkers and three-dimensional echocardiogram in monitoring cardiac toxicity.

Conflict of interest

The authors declare no conflicts of interest.

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