Cardiotoxicity and Cancer Therapy: Treatment-Related Cardiac Morbidity in Patients Presenting with Symptoms Suggestive of Heart or Lung Disease

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Key Words

Anthracyclines · Cardiotoxicity · Chemotherapy · Heart disease · Natriuretic peptides · Radiotherapy

Abstract

Objectives: Cardiac injury is one of the complications of cancer treatment. This study aimed to investigate the relationships between the types of radiotherapy of the chest (RT), chemotherapy (CT), cancer surgery (CS) and endocrine therapy (ET), and the presence of heart disease, and their associations with the serum level of N-terminal pro-B-type natriuretic peptide (NT-proBNP). **Methods:** A consecutive series of 374 patients with cancer who were referred because of symptoms suggestive of heart or lung disease prospectively underwent a diagnostic workup. **Results:** The prevalence of heart disease was 36.9%. RT administered before 1995 (n = 19) was associated with both increased odds of heart disease [adjusted odds ratio 10.3, 95% confidence interval 3.1–34.0] and higher ln-transformed NT-proBNP values (p < 0.01) compared to the control group (no RT or RT for right-

sided breast cancer from 1995 onwards; n = 311). Anthracycline-treated patients (n = 54) had higher adjusted values for ln(NT-proBNP) compared to the control group (no CT; n = 243; p < 0.01) but no increased odds of heart disease. **Conclusions:** While pre-1995 RT and anthracycline-containing CT were associated with cardiac effects, there was no evidence that RT using modern cardioprotective techniques, CT in the absence of anthracyclines, CS or ET had detrimental effects on the heart.

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Introduction

Advances in cancer management have improved long-term survival rates. The cardiac side effects of cancer therapies, which often manifest years after treatment, have therefore become more important [1]. The

This paper is dedicated to the memory of Friedrich Hirsch.

Table 1. Definition of treatment strata

Treatment	Stratum 1	Stratum 2	Stratum 3	Stratum 4
RT	no RT or RT from 1995 onwards for right-sided breast cancer ² (n = 311)	RT from 1995 onwards for left-sided breast cancer ² (n = 24)	RT from 1995 onwards ¹ but not for breast cancer (n = 20)	RT before 1995 ³ (n = 19)
CT (or immunotherapy)	no CT (n = 243)	CT without anthracyclines (n = 77)	CT with anthracyclines (n = 54)	
CS	no CS or endoscopic tumor resection only (n = 124)	other CS (n = 115)	prostatectomy (n = 33)	laparotomy or thoracotomy (n = 102)
ET	no ET (n = 295)	any ET (n = 79)		

Numbers of patients are shown in parentheses. Patients presenting with 2 different types of RT or CS were assigned the higher stratum.

¹ Computed tomography-based 3-dimensional RT planning with individual shields; 6- or 18-MV photon beam; total dose: 30–40 (lymphoma) and 50–66 Gy (lung cancer).

² The radiation dose was 50–60 Gy, 5 × 1.8–2.0 Gy/week.

³ Photon beam radiotherapy via opposing rectangular fields without computed tomography-based planning or dosimetry; lymphoma: anterior-

posterior posterior-anterior isocentric opponent fields, total dose 40 Gy, 5 × 2 Gy/week; individual lung shields; 6- or 18-MV photon beam; lung cancer: anterior-posterior posterior-anterior isocentric opponent fields, total dose 50–60 Gy, 5 × 2 Gy/week; spinal cord shield >40 Gy; 6- or 18-MV photon beam; breast cancer: tangential isocentric opponent rectangle fields; total dose 50 + 10 Gy boost, 5 × 2 Gy/week; 6- or 18-MV photon beam; boost: electrons of appropriate energy.

assessment of cardiotoxicity frequently revolves around the indices of left ventricular systolic function. While easy to measure, parameters such as ejection fraction have their limitations [2, 3]. Furthermore, cardiac injury is often not limited to the myocardium. Following radiotherapy of the chest (RT), for instance, other parts of the heart may be involved, too [4, 5]. Therefore, the term ‘cardiotoxicity’ should be more inclusive. Although many cancer therapies are multimodal, most previous studies have focused on the cardiac effects of one treatment aspect [6, 7]. We chose a more comprehensive approach and aimed to study the effects of RT, chemotherapy (CT), cancer surgery (CS) and endocrine therapy (ET) in terms of cardiotoxicity in patients who were referred for an evaluation by a cardiologist or a pulmonologist because of symptoms suggestive of heart or lung disease.

Patients and Methods

Patients

This prospective single-institution study included 376 consecutive outpatients with a history of previous or active malignant disease who were referred from primary care, oncology and radiooncology to the cardiology or pulmonology services of an academic teaching hospital from May 2007 to September 2011 to evaluate dyspnea, chest pain, pulse irregularities, cough or exercise intolerance. We had to exclude 2 cases because of missing data, leaving 374 patients with 424 malignant diseases for the final anal-

ysis. All self-reported diagnoses and treatments were verified by reviewing the patients’ records. The study was approved by the Ethics Committee of the Baden-Wuerttemberg State Chamber of Physicians.

Diagnostic Procedures and Patient Classification

The patients underwent an examination for heart and lung disease that included electrocardiography, echocardiography, chest X-ray and pulmonary function testing, as previously described [8].

A diagnosis of heart disease was made in the presence of at least one of the following findings: (1) impaired left ventricular systolic function (ejection fraction <50% determined by the biplane modified Simpson’s rule); (2) atrial fibrillation; (3) left bundle branch block, (4) pulmonary hypertension (peak systolic gradient across the tricuspid valve measured with continuous-wave Doppler ≥35 mm Hg); (5) at least mild aortic stenosis (mean pressure gradient ≥20 mm Hg), at least moderate aortic regurgitation, at least moderate mitral regurgitation, at least mild mitral stenosis or severe tricuspid regurgitation, and (6) angiographically proven coronary disease or a hospital diagnosis of previous myocardial infarction. The patients were categorized into prospectively defined strata according to the type of RT, CT, CS and ET (table 1). Blood samples were assayed for N-terminal pro-B-type natriuretic peptide (NT-proBNP; ELISA test; Roche Diagnostics, Mannheim, Germany). The lower limit of detection of C-reactive protein (CRP) was 0.71 mg/l. A value of 0.35 mg/l was assigned to the 22 patients with undetectable CRP levels. The estimated glomerular filtration rate (eGFR) was calculated [9], and the eGFR values were categorized according to the National Kidney Foundation (NKF) strata.

Data Analysis

Logistic regression analysis was used to evaluate associations, given as an odds ratio (OR) and 95% confidence interval (CI), between the 4 RT strata and the prevalence of heart disease. The

Table 2. Distribution of heart and lung disease and the values for NT-proBNP in the whole study group and according to disease groups

Characteristics	Total group 374 patients with 424 tumors	Disease groups				
		90 lung cancers (90 patients)	96 breast cancers (90 patients)	50 prostate cancers (50 patients)	58 lymphomas (58 patients)	130 other cancers (127 patients)
<i>Patient characteristics</i>						
Age at referral, years	68.0±11.2	67.4±9.9	66.9±9.8	72.7±7.6	65.2±15.2	69.0±11.3
BMI, kg/m ²	27.9±5.4	27.9±5.6	27.7±5.0	28.7±5.5	27.0±5.3	28.3±5.6
Females, %	48.9	30.0	100.0	0.0	55.2	44.1
Arterial hypertension, %	61.8	64.4	58.9	72.0	50.0	66.1
Diabetes, %	16.3	21.1	11.1	20.0	10.3	20.5
Ever smoker, %	48.4	80.0	28.9	54.0	32.8	46.5
Pack-years	0 (0–30)	40 (10–60)	0 (0–5)	5 (0–30)	0 (0–10)	0 (0–30)
eGFR, ml/min/1.73 m ²	84 (69–96)	89 (72–104)	87 (68–95)	84 (75–93)	80 (62–97)	80 (65–93)
Hemoglobin, g/dl	13.5±1.7	13.6±1.9	13.1±1.5	14.3±1.6	13.3±1.7	13.5±1.6
CRP, mg/l	4.30 (1.80–9.90)	8.20 (4.00–26.80)	3.20 (1.60–6.50)	2.60 (1.30–8.10)	3.60 (1.60–10.00)	4.10 (1.80–8.00)
Active disease, %	33.4	61.1	21.1	10.0	50.0	15.0
<i>Heart disease, %</i>	36.9	40.0	30.0	44.0	36.2	37.8
Impaired LV systolic function	5.9	10.0	3.3	6.0	6.9	4.7
Atrial fibrillation	17.1	16.7	13.3	24.0	17.2	15.0
Left bundle branch block	0.8	0.0	2.2	0.0	0.0	0.8
Pulmonary hypertension	13.1	11.1	17.8	8.0	13.8	12.6
Valvular disease	8.0	5.6	12.2	6.0	10.3	7.9
Coronary disease	10.2	8.9	5.6	16.0	8.6	12.6
<i>Nonmalignant lung disease, %</i>	60.2	72.2	53.3	64.0	55.2	59.1
COPD	17.7	40.0	7.8	16.0	6.9	17.3
Asthma	32.4	18.9	37.8	42.0	32.8	33.9
Other	16.3	23.3	12.2	8.0	24.1	12.6
<i>Neither heart nor lung disease, %</i>	26.2	22.2	30.0	22.0	29.3	25.2
<i>NT-proBNP, pg/ml (all patients)</i>	175 (75–535)	219 (63–709)	160 (79–353)	191 (80–499)	248 (107–748)	151 (66–516)
Without heart disease (n = 236)	96 (52–203)	78 (46–250)	105 (65–178)	89 (52–209)	191 (76–277)	85 (47–174)
With heart disease (n = 138)	761 (279–1,663)	905 (271–1,511)	1,099 (261–2,007)	453 (191–793)	1,051 (305–1,852)	574 (268–1,391)

Results are expressed as means ± SD or medians (interquartile ranges). Active disease: residual tumor or time interval between surgery/end of chemotherapy/radiotherapy and referral <3 months; lymphoma: Hodgkin's disease (11 patients), non-Hodgkin lymphomas including multiple myeloma (33) and chronic lymphocytic leukemia (14), other cancers: ovary (11), renal/urothelial (26), colon (30), stomach (2), chorion (1), uterus/cervix (16), skin (14), thymus (1), thyroid (5), brain (1), larynx/pharynx/oral cavity (7), pleu-

ra (2), liver (1), bone (2), testicle (7), esophagus (3), cancer of unknown primary (1); other nonmalignant lung disease: interstitial lung disease (23), restrictive disorder following pulmonary resection (16), hypercapnic respiratory failure (6), disorders of the chest wall or pleural disease (18) and narrowing of the central airways (7). COPD = Chronic obstructive pulmonary disease; LV = left ventricular.

patients assigned to RT stratum 1 served as the reference group. This association was tested in 3 models: unadjusted models; partially adjusted models that controlled for age and body mass index (BMI) as continuous variables, and sex, diabetes, arterial hypertension and smoking history (ever smoker, pack-years) as categorical variables, and fully adjusted models that also included the CT, CS and ET stratum memberships [10]. The same approach was adopted to assess the effect of CT using CT stratum 1 as the reference group and controlling for RT, CS and ET stratum membership in the fully adjusted model. Multiple linear regression models were used to evaluate the effect of RT stratum membership on the logarithmically transformed NT-proBNP values [ln(NT-proBNP)]. The baseline covariates considered were age, BMI, the ln-transformed CRP level, hemoglobin level, sex, the NKF stages of eGFR and the presence of arterial hyper-

tension. The fully adjusted models also controlled for CT, CS and ET stratum membership. Similarly, the effect of CT stratum membership on ln(NT-proBNP) was analyzed by adjusting for RT, CS and ET stratum membership in the fully adjusted model. Interaction terms were incorporated to determine whether the presence of arterial hypertension interfered with the effects of pre-1995 RT or anthracyclines on the outcome variables. Differences with variables between strata were examined by the two-sample t test or the χ^2 test, as appropriate. Given the exploratory nature of the study, the test results should not be interpreted as confirmatory, and no adjustment for multiple testing was made. A value of $p < 0.05$ was considered significant. The analyses were performed using SAS, version 9.2 (SAS Institute, Chicago, Ill., USA).

Table 3. Treatment according to disease groups

Treatment	All tumors (n = 424)	Lung cancer (n = 90)	Breast cancer (n = 96) (51/45)	Prostate cancer (n = 50)	Lymphoma (n = 58)	Other cancer (n = 130)
RT, %	22.9	13.3	67.7 (76.4/57.8) ¹	2.0	25.9	3.1
Since 1995	18.4	11.1	59.4 (64.7/53.3)	2.0	13.8	1.5
Before 1995	4.5	2.2	8.3 (11.8/4.4)	0.0	12.1	1.5
CT (or immunotherapy), %	32.1	20.0	41.7	0.0	70.7	27.7
Anthracyclines	12.7	2.2	29.2		37.9	1.5
Alkylating agents	24.3	16.7	31.3		60.3	16.2
Antimetabolites	11.6	6.7	17.7		8.6	14.6
Microtubule-targeting drugs	17.2	16.7	22.9		41.4	8.5
Molecular-targeting agents	3.3	3.3	8.3		0.0	2.3
Rituximab	6.1	0.0	0.0		44.8	0.0
Other	1.9	1.1	0.0		8.6	1.5
CS, %						
Thoracotomy	9.4	38.9			3.4	2.3
Laparotomy	14.9	0			8.6	44.6
Prostatectomy	8.5			72.0		
Other	32.5		99.0	0.0	1.7	32.3
No CS or endoscopic resection only	34.7	61.1	1.0	28.0	86.2	20.8
ET, %	19.1	0.0	67.7	30.0	0.0	0.8
Aromatase inhibitors	11.1		47.9	0.0		0.8
Estrogen receptor modulators	6.1		25.0	0.0		0.0
Antiandrogens	9.4		0.0	8.0		0.0
GRH agonists	4.0		6.3	20.0		0.0

¹ All cases (right breast/left breast). GRH = Gonadotropin-releasing hormone.

Results

Table 2 lists the clinical data, the NT-proBNP values and the distribution of the cardiac and pulmonary findings in the whole study group and in each disease group. The types of treatment according to disease group are presented in table 3. The prevalence values of heart disease were 35.1 and 39.1% in RT stratum 1 and CT stratum 1, respectively.

The median (interquartile range) time intervals between RT and referral were 5.6 (1.2–8.5) years in RT stratum 2, 2.6 (0.5–8.8) years in RT stratum 3 and 20.2 (16.5–28.9) years in RT stratum 4, respectively. Membership in RT stratum 4 was associated with increased odds of valvular heart disease (OR 6.4, 95% CI 2.2–18.5) and coronary disease (5.3, 95% CI 1.9–15.1), whereas the odds of impaired left ventricular function were not affected. Only 2 of the 19 patients assigned to RT stratum 4 exhibited impaired left ventricular function. Overall, there were higher odds of heart disease in RT stratum 4

compared with RT stratum 1 in the unadjusted analysis (OR 5.2, 95% CI 1.8–14.8). Figure 1 shows that the strength of this association increased after adjustment for baseline characteristics (OR 10.4, 95% CI 3.2–34.6) and in the fully adjusted model (OR 10.3, 95% CI 3.1–34.0). The effect of RT stratum 4 membership on the odds of heart disease was not modified by any other cancer therapy. The presence of diabetes (OR 2.0, 95% CI 1.1–3.8) and older age ($p < 0.01$) were the only covariates associated with higher odds of heart disease in the fully adjusted model. The values for NT-proBNP [median (interquartile range)] were higher in RT stratum 4 than stratum 1 [636 (301–1,526) vs. 163 (69–483) pg/ml, $p < 0.01$], whereas RT stratum 2 and 3 did not differ from RT stratum 1 in this regard. The regression analyses confirmed the effect of RT stratum 4 membership on NT-proBNP (fig. 2).

The odds of heart disease were not different among the 3 CT strata (fig. 3). Impaired left ventricular function was found in 7.4% of the anthracycline-treated patients and

Fig. 1. Association between the type of RT and the odds of heart disease compared to the reference group in unadjusted, partially adjusted (for age, BMI, sex, smoking history and the presence of diabetes or arterial hypertension) and fully adjusted (also adjusted for the type of CT, CS and ET) models. The reference group (RT stratum 1) includes patients with no RT or RT for right-sided breast cancer from 1995 onwards. RT strata 2–4 are defined as shown in table 1. ORs are plotted on a logarithmic scale. The bars represent the 95% CIs.

Fig. 3. Association between the type of CT and the odds of heart disease in unadjusted, partially adjusted (for age, BMI, sex, smoking history and the presence of diabetes or arterial hypertension) and fully adjusted (also adjusted for the type of RT, CS and ET) models. The ORs are plotted on a logarithmic scale. The bars represent the 95% CIs. The reference group (CT stratum 1) consists of patients with no previous CT. CT strata 2 and 3 are defined as shown in table 1.

Fig. 2. Relationship between RT stratum membership (table 1) and ln(NT-proBNP) in unadjusted, partially adjusted (for age, BMI, CRP and hemoglobin level, sex, NKF stages of eGFR and the presence of arterial hypertension) and fully adjusted (also adjusted for the type of CT, CS and ET) models. The bars represent the 95% CIs. * $p < 0.01$ vs. the control group (RT stratum 1).

Fig. 4. Relationship between CT stratum membership (table 1) and ln(NT-proBNP) in unadjusted, partially adjusted (adjusted for age, BMI, CRP level, hemoglobin level, sex, NKF stages of eGFR and the presence of arterial hypertension) and fully adjusted (also adjusted for the type of RT, CS and ET) models. The bars represent the 95% CIs. * $p < 0.01$ vs. CT stratum 1.

6.6% of the patients assigned to CT stratum 1. The median time interval between treatment with anthracyclines and referral was 6.8 (3.6–12.1) years. Figure 4 shows that the effect of anthracyclines on NT-proBNP became apparent only in the adjusted models. In addition to CT stratum 3 and RT stratum 4 membership, the following covariates were also associated with increased NT-proBNP levels: older age, lower BMI, lower hemoglobin level, higher NKF stage of eGFR and the presence of arterial hypertension. The anthracycline-treated patients were younger (61.1 vs. 70.0 years, $p < 0.01$), had higher eGFR values (90.2 vs. 82.1 ml/min per 1.73 m², $p < 0.05$) and a lower prevalence of arterial hypertension (40.7 vs. 67.5%, $p < 0.01$) than the patients assigned to CT stratum 1. The presence of arterial hypertension did not augment the effect of RT stratum 4 and CT stratum 3 membership on the odds of heart disease or NT-proBNP, respectively. The prevalence of arterial hypertension increased with age and BMI in both sexes and was not associated with ET stratum membership. CS and ET stratum membership had no effect on NT-proBNP levels and the odds for heart disease.

Discussion

Among the 13 treatment strata, cardiac effects could only be demonstrated for RT administered before 1995 and anthracycline-containing CT. Whether RT applied before 1995 and CT with anthracyclines have additive effects cannot be determined from our data because only 4 of the 19 patients assigned to RT stratum 4 had also been treated with anthracyclines. High blood pressure is a frequent condition in patients with cancer [11]. In this study, the prevalence of hypertension was 61.8%. Our findings do not suggest that hypertension increases the risk of cardiotoxicity associated with pre-1995 RT or anthracycline-containing CT.

The patients were not assessed before and after a specific anticancer therapy. This was an observational study that only included patients with symptoms suggestive of heart or lung disease. These entry criteria accurately reflect the everyday practice of the referring physicians and are critical for interpreting our results. An asymptomatic survivor of cancer is less likely to have treatment-related heart disease and, therefore, less likely to be referred for evaluation by a cardiologist. As a result, this real world study overestimates the cardiotoxicity of anticancer therapy relative to the overall population of treated patients. However, if no cardiac effect can be

demonstrated even in this group of symptomatic patients, significant cardiotoxicity of a given treatment is rather unlikely.

The year 1995 was prospectively chosen as the cutoff between RT stratum 4 and the other RT strata because cardioprotective techniques with the use of computed tomography-assisted 3D dosimetry rapidly became established in this area in the mid-1990s. Stratification by a specific year implies a certain degree of overlap that might have distorted our findings. Adjustments for the radiation dose administered to the heart or the irradiated area are principally not possible in RT stratum 4. In RT strata 2 and 3, these covariates could not be controlled for because of the low sample size in both cohorts. This weakness of our study limits its ability to detect detrimental effects of modern cardioprotective RT.

Our study has further limitations. First, the median time interval between CT and referral was only 3.2 years in CT stratum 2. A follow-up study in 5-year survivors of testicular cancer suggested that CT with cisplatin, vinblastine and bleomycin was associated with a 1.9-fold increased risk of myocardial infarction [12]. In patients receiving RT after 1995, the median time intervals between RT and inclusion in the study were also relatively short. The risk of heart disease following RT begins to rise within the first 5 years after exposure and continues to increase with time, even decades after treatment [13, 14]. Therefore, our findings should be interpreted with caution; the patients assigned to CT stratum 2 or RT stratum 2 or 3 may manifest cardiac damage at a later time. Second, the outcome variables were not adjusted for the anthracycline doses, because these data were not available to us in all cases. All RTs and CTs had been administered at university medical centers and academic teaching hospitals, so a high level of adherence to the treatment guidelines can be assumed. Third, only 14 patients were treated with molecular-targeting agents, 6 of whom had also received anthracyclines. Therefore, we cannot answer the question of whether molecular-targeted therapy amplified the effect of anthracyclines on NT-proBNP. Sample size problems also precluded a separate evaluation of the cardiac effects produced by the agents assigned to CT stratum 2 and the different types of endocrine interventions (table 3). Fourth, parameters of diastolic function were not used for diagnosing heart disease because tissue Doppler imaging was not available to us before 2008 [15].

Our results show that impaired systolic function of the left ventricle is a rare finding, even in patients who received pre-1995 RT or anthracycline-containing CT;

neither of the 2 strata was associated with systolic dysfunction. Cardiac damage due to RT with outdated techniques often manifests itself in other ways. The increased odds of valvular and coronary disease observed in RT stratum 4 are consistent with previous reports [16, 17]. The serum level of NT-proBNP is not only elevated in systolic dysfunction, but also in an array of heart disease so that this marker has gained acceptance as a quantitative marker of cardiac stress [18]. Therefore, NT-proBNP holds promise as a biomarker of cardiotoxicity, but its role in detecting cardiac damage caused by cancer treatment is still unclear [19–21]. One reason for this may be that numerous extracardiac covariates influence the NT-proBNP level. Low BMI, low hemoglobin levels and impaired renal function were associated with elevated NT-proBNP levels. These determinants are often abnormal in cancer patients, hindering the interpretation of a given NT-proBNP value in the individual patient. Our results illustrate that false conclusions could be drawn if these influences were ignored: CT strata 1 and 3 were not equally balanced with respect to 3 covariates that significantly influenced the NT-proBNP level. This imbalance reduced the NT-proBNP level in CT stratum 3. Therefore, the unadjusted values for NT-proBNP did not differ between the 2 strata, and the anthracycline-mediated increase in NT-proBNP levels be-

came evident only after adjustment. The effect of previous CT with anthracyclines on the $\ln(\text{NT-proBNP})$ values is not trivial. Anthracycline use had the same effect as a 16.7-year increase in age, a BMI decrease of 13.0 and a 3.6 g/dl decrease in hemoglobin. Previous CT with anthracyclines increased the NT-proBNP levels 1.6-fold more than the presence of arterial hypertension. The effect of pre-1995 RT was even more pronounced. Moving from RT stratum 1 to 4 increased the $\ln(\text{NT-proBNP})$ levels 1.9-fold more than moving from CT stratum 1 to 3.

In conclusion, this study suggests that pre-1995 RT and anthracycline-containing CT are associated with cardiac injury in symptomatic patients referred for cardiac or pulmonary evaluation. By contrast, no adverse cardiac effects could be demonstrated for RT from 1995 onwards and CT regimens not including anthracyclines. Given the high prevalence of cardiovascular disease among cancer patients with symptoms suggestive of heart or lung disease, oncologists, radiooncologists and cardiologists should collaborate closely.

Disclosure Statement

The authors have no conflict of interest to disclose.

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