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Original article

Brain natriuretic peptide as a cardiac marker of transient radiotherapy-related damage in left-sided breast cancer patients: A prospective study

I. Palumbo [a, *], B. Palumbo [b], M.L. Fravolini [c], M. Marcantonini [d], E. Perrucci [e], M.E. Latini [f], L. Falcinelli [e], I. Sabalich [b], C. Tranfaglia [b], G. Schillaci [g], E. Mannarino [h], C. Aristei [a]

[a] Radiation Oncology Section, University of Perugia, Perugia General Hospital, Perugia, Italy
[b] Nuclear Medicine and Health Physics Section, University of Perugia, Perugia, Italy
[c] Department of Engineering, University of Perugia, Italy
[d] Medical Physics Unit, Perugia General Hospital, Perugia, Italy
[e] Radiation Oncology Division, Perugia General Hospital, Perugia, Italy
[f] Radiology Division, Perugia General Hospital, Perugia, Italy
[g] Internal Medicine Unit, Department of Medicine, University of Perugia, Italy
[h] Internal Medicine, Angiology and Arteriosclerosis Diseases Unit, Department of Medicine, University of Perugia, Italy

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ABSTRACT

Purpose: Our study evaluated brain natriuretic peptide (BNP) changes over time after adjuvant radiotherapy (RT) in women with left-sided breast cancer investigating its correlation with heart dosimetric parameters.

Methods: Forty-three patients underwent clinical cardiac examination, electrocardiogram (ECG), echocardiography and BNP measurement before RT (T0) and 1 (T1), 6 (T6) and 12 months (T12) after. After T12 cardiac assessment was performed annually in each patient. Mean values and standard deviation (SD) of BNP, left ventricular ejection fraction (LVEF), V20, V25, V30, V45 and mean dose were calculated. Normalized BNP (BNPn) was calculated as follows: BNPnT1 = BNPT1/BNPT0, BNPnT6 = BNPT6/BNPT0, BNPnT12 = BNPT12/BNPT0. Absolute BNP and BNPn values were used for data analysis.

Results: Median follow-up from the end of RT to the last check-up was 87 months (range 37–120 months). Minimum follow-up was 74 months except for two patients, who died at respectively 37 and 47 months after RT. In all patients LVEF did not change significantly ($p = 0.22$) after RT. BNP increased significantly ($p < 0.001$), particularly 1 and 6 months after RT. It slightly decreased after 12 months. BNP did not correlate with V20, V25, V30, V45, mean dose and MHD. All BNPn correlated significantly ($p < 0.05$) with V20, V25, V30, V45, mean dose and MHD. Four patients had a cardiac event; in the only subject who developed myocardial infarction, V20, V25, V30 and V45 were the highest and BNP increased from T1 and persisted high even at T12.

Conclusion: Our results confirm that BNP could be a useful minimally invasive marker of early RT related cardiac impairment.

Abbreviations: BNP, natriuretic peptide; RT, radiotherapy; BNPn, normalized BNP; BCS, breast conserving surgery; CHF, congestive heart failure; CAD, coronary artery disease; MI, myocardial infarction; ACS, acute coronary syndrome; ESMO, European Society for Medical Oncology; ECOG, Eastern Cooperative Oncology Group; HT, hormonal therapy; 3D, three-dimensional; CT, computed tomography; CTV, clinical target volume; OAR, organs at risk; NTCP, normal tissue complication probability; TPS, treatment planning system; DVH, dose-volume histograms; MHD, maximum heart distance; DRRs, digital reconstructed radiographs; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; LAD, left anterior descending; IMRT, intensity modulated radiation therapy; PBI, partial breast irradiation; PRV, planning organ at risk; BED, biological effective dose.

* Corresponding author. Radiation Oncology Section, Department of Surgical and Biomedical Sciences, University of Perugia, Perugia General Hospital, 06156 Perugia, Italy. Tel./fax: +39 0755783254.
E-mail address: isabella.palumbo@unipg.it (I. Palumbo).

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Introduction

Post-operative radiotherapy (RT) after breast conserving surgery (BCS) is the standard treatment for patients with early stage breast cancer. Due to now obsolete techniques mainly in the left breast, post-operative RT, particularly after mastectomy, was associated with increased cardiovascular mortality [1] which is nowadays greatly reduced with modern irradiation techniques [2].

Cardiotoxicity is a major issue in left-sided breast cancer patients [3], particularly when, besides RT, they are treated with chemotherapeutic agents like anthracyclines, taxanes and/or trastuzumab which are cardiotoxic. Consequently, to minimize toxicity the multidisciplinary care team needs to focus in optimal chemo-radiotherapy sequencing [4] and radiation oncologists have to use approaches such as intensity modulated radiation therapy (IMRT), proton beam irradiation, prone positioning and breath hold [5,6]. Furthermore partial breast irradiation (PBI), an alternative to whole irradiation after BCS in selected patients [7], may reduce dose to the heart in those with left breast cancer [8].

RT can induce as acute effects pericarditis, pericardial effusion, myocarditis, left ventricular dysfunction and arrhythmias, while as late effects congestive heart failure (CHF), ischemia, coronary artery disease (CAD), myocardial infarction (MI), atherosclerosis and valvular dysfunction [9–11]. The severity of radiation-related cardiotoxicity, which is caused by damage to micro- and macro-vasculature, is linked to the heart-absorbed dose [11]. Although a potential increase in cardiac events was described after RT, the available studies do not consider the impact of newer commonly utilized RT techniques which allow heart sparing [12]. However, as only few data on late cardiac events are available due to the lack of long-term follow-ups, the correlation between the dosimetric parameters and cardiac events is still clearly not defined.

Since detecting early cardiac injury is crucial for prompt therapy, several markers of cardiac impairment are under investigation [13].

Brain Natriuretic Peptide (BNP) is secreted by ventricles in response to myocyte stretch. Probably as a consequence of left ventricle impairment it is elevated in heart failure and in the acute coronary syndrome (ACS) which includes acute MI and unstable angina [14–18]. Indeed, the European Society for Medical Oncology (ESMO) suggests measuring BNP in clinical trials that evaluate cardiotoxicity during and after anti-cancer therapy [19]. As BNP is a marker of ventricles myocyte impairment it could probably indicate an early RT-related cardiac damage, that is an effect of indirect myocyte toxicity secondary to microvascular damage and ischemia [10], that has been shown even at 6 months after the end of RT [20].

Only few studies however, showed temporal rises in BNP and its precursor pro-B-type Natriuretic Peptide (NT-pro-BNP) after RT [21–24]. In particular three papers [22–24] evaluated patients with left breast cancer.

Our prospective study is however, to our knowledge, the only one that enrolled chemotherapy–naïve left breast cancer patients treated with BCS followed by RT (using the same schedule in the same volumes) with long-term follow-ups.

The aim of our study was to investigate BNP changes before and over time after RT and to correlate them with heart dosimetric parameters in order to identify an early marker of RT-related cardiac damage.

Materials and methods

From February 2004 to October 2008, 43 female patients aged 37–81 years (median, 63 years) with left breast cancer who received BCS followed by external beam RT were enrolled in the study which was approved by the Umbria Region Public Health Ethics Committee and conducted in accordance with the Helsinki Declaration of 1975 as revised in 2000. Written informed consent was obtained from each patient.

Inclusion criteria were female gender, histological diagnosis of cancer in the left breast, BCS, Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2. Exclusion criteria were CAD, a history of stroke or chronic kidney disease (serum creatinine > 132 μmol/L) and other concomitant diseases that could influence BNP, adjuvant and neo-adjuvant chemotherapy and anti-Her2 therapy. Thirty-two (74.42%) patients with positive estrogen and/or progesterone receptor status received hormonal therapy (HT): 15 (46.87%) tamoxifen, 6 (9.37%) anastrozole, 3 (18.75%) letrozole, 7 (21.87%) tamoxifen plus LH-RH analog and 1 (3.12%) letrozole plus LH-RH analog.

Cardiovascular risk factors such as smoking, arterial hypertension, serum cholesterol, serum triglycerides, diabetes, obesity, and family history of CAD were assessed in all patients (Table 1). Each patient underwent clinical cardiac examination, electrocardiogram (ECG), echocardiography and BNP determination before RT (T0) and 1 month (T1), 6 months (T6) and 12 months (T12) after the end of RT. Throughout the follow-up each patient underwent breast cancer check-ups in accordance with standard guidelines [25] and an annual cardiac assessment.

Radiotherapy

Three-dimensional (3D) conformal RT was delivered to the left breast with two tangential fields using a 4 MV linear accelerator (Varian Clinac 600, Varian, Palo Alto, CA, USA) and standard fractionation in all cases: 50 Gy in 25 fractions was prescribed for 38 patients, while 50.4 Gy in 28 fractions was administered to 5 patients with large breasts. A boost dose of 10–20 Gy in 2 Gy daily fractions was delivered using 4 MV photon beams to the tumoral bed in 32 patients. The computed tomography (CT) scan (Lightspeed QX/I, GE Healthcare) was carried out without intravenous contrast with 5 mm slice thickness and step. Contouring of the left breast (clinical target volume, CTV), left lung and the heart (organs at risk, OAR) by one radiation oncologist, who is expert in breast cancer treatment, was confirmed by an expert radiologist. Whole heart contouring included the left atrium, left ventricle, right atrium, right ventricle and pericardium, and excluded large blood vessels (pulmonary trunk, ascending aorta and superior vena cava).

Normal tissue complication probability (NTCP) for late cardiac toxicity was calculated for each patient by our treatment planning system (TPS Pinnacle^3 Philips). Dose-volume histograms (DVH) for the treatment plans were evaluated and dose-volume specifications for the heart were: V20, V25, V30, V45 (that is the heart volume percentage receiving ≥20 Gy, ≥25 Gy, ≥30 Gy and ≥45 Gy respectively) and mean dose. The maximum heart distance (MHD) from the posterior edge of the tangent field to the heart contour, was calculated using digital reconstructed radiographs (DRRs).

BNP measurement

Blood tests were performed at 8 am the day patients underwent ECG and echocardiography. Blood was drawn from a forearm vein after a 14-h overnight fast, collected into ethylenediaminetetraacetic acid 1.5 mg/ml tubes. Plasma was separated by centrifugation at 2000 g (2–8 °C for 5 min) and BNP measured by the immunoradiometric method (Shinoria-BNP, CIS Bio International-Schering, Gif/Yvette, France) in duplicate for each patient. Intra- and inter-assay variations of the test were <4% and 8%, respectively; sensitivity was 2.0 pg/ml, and the degree of cross reactivity with human plasma atrial natriuretic peptide was $<1.10^{-5}$%. Normal BNP levels in women according to the test's manufacturer were 6.7 ± 18.6 pg/ml. BNP was determined at T0, T1, T6 in all patients. At T12 11/43 patients refused blood sampling.