Iodine-123 metaiodobenzylguanidine in the assessment of late cardiac effects from cancer therapy

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Abstract. Recognition of adverse late cardiac effects from cancer therapy may enable identification of patients with risk of cardiotoxicity upon cancer retreatment. In this study the feasibility of using iodine-123 metaiodobenzylguanidine (123I-MIBG) heart scintigraphy to detect abnormalities of the myocardial adrenergic neurone function in the late period after cancer therapy was evaluated in relation to the left ventricle ejection fraction (LVEF) in 18 cancer patients: 11 had undergone thoracic irradiation involving the heart, in five cases in combination with anthracycline therapy, 11–228 months (median 60 months) before radionuclide tests, while seven had not received previous anthracycline and/or radiotherapy (controls). The 123I-MIBG cardiac uptake, expressed as a heart-to-mediastinum ratio on planar images after 4 h, ranged from 1.21 to 1.76 (median 1.56) in cancer therapy patients, which was significantly decreased (P=0.0006) in comparison with controls (range 1.81–2.06, median 1.9). The myocardial 123I-MIBG washout, calculated from planar images after 15 min and 4 h, and LVEF also showed significant differences, but with some overlap in individual cases. In cancer therapy patients, cardiac abnormalities seen on planar images and additional single-photon emission tomographic images varied from focal defects to diffusely reduced myocardial uptake. It is concluded that 123I-MIBG heart scintigraphy, which is able to identify cardiac adrenergic neurone abnormalities in the follow-up period after cancer therapy, may help to identify relapsed patients who are at increased risk of developing cardiotoxicity during retreatment with cardiotoxic therapy modalities.

Key words: Late cardiac effects – Anthracyclines – Radiotherapy – Iodine-123 metaiodobenzylguanidine heart scintigraphy


Introduction

The diagnostic study of organ injury due to cancer therapy has gained in importance recently due to the increasing number of long-term survivors after cancer treatment (particularly patients with haematological malignancies such as lymphomas and certain leukaemias) [1, 2]. With the combined use of surgery, radiotherapy and chemotherapy, approximately 65% of children and adolescents who are diagnosed with cancer will be cured of their disease. In the United States it has been predicted that, by the year 2010, one in every 250 young adults under the age of 45 years will be a survivor of childhood malignancy [3]. Most of them will have received treatment known to be associated with cardiotoxicity.

Late adverse cardiac effects of cancer therapy are principally related to anthracycline-containing chemotherapy regimens and to radiotherapy involving the heart. In two large series of paediatric long-term survivors who were treated with anthracyclines [2, 4], an incidence of late cardiac abnormalities, assessed by echocardiography, of 23%–57% was reported, including abnormalities in fractional shortening, afterload or contractility of the left ventricle. Cardiac dysfunction appears to increase with time after completion of anthracycline therapy and overt congestive heart failure often occurs only after 10 years [4]. In a large series of patients treated for Hodgkin’s disease, mediastinal irradiation was also shown to significantly increase the risk of death from cardiac disease within 5 years after irradiation [5]. In another investigation, cardiac abnormalities were noted in 23.8% of patients who received left breast irradiation...
tion, including the internal mammary chain, but in only 5.4% of patients who did not receive irradiation [6]. Although irradiation to the cardiac area may cause a broad spectrum of late effects affecting the pericardium, myocardium, endocardium, conduction system, coronary arteries and small vessels, the damage appears essentially to be based on slowly evolving endothelial cell injury resulting in a loss of capillaries, probably ischaemia at the microcirculatory level, fibrosis and progressive cardiac dysfunction [7]. On the other hand, anthracycline-related injury involves predominantly the myocyte and may severely limit myocardial growth in childhood: a lifelong reduction in myocardial mass may occur, resulting in a long-term decrease in cardiac reserve [2]. The pathology noted on late cardiac biopsy comprises mainly cardiac fibrosis; the myocyte vacuolization that is seen on biopsy specimens during or soon after therapy is less prominent [4].

The observation that in many patients treatment-related late cardiac sequelae can be detected at a subclinical level [2, 4], which may signify an increased risk at retreatment for cancer recurrence with potentially cardiotoxic therapy modalities, led us to explore the feasibility of heart scintigraphy with iodine-123 metiodobenzylguanidine (123I-MIBG) for the detection of abnormalities of the myocardial adrenergic neurone function during follow-up after cancer therapy. The selection of 123I-MIBG for this purpose was based on the laboratory and clinical evidence that anthracyclines may alter the myocardial adrenergic neurone function and the MIBG parameters [8–10] as well as on the laboratory evidence of a time/dose-dependent reduction in myocardial noradrenaline concentration in the late post-irradiation period [11]. Finally, late cardiac sequelae of both anthracycline-containing chemotherapy and radiotherapy appear to lead to a progressive loss of cardiac function [4], which may also imply alterations in the adrenergic support of the heart. In this paper, the findings of 123I-MIBG heart scintigraphy together with the evaluation of the left ventricle ejection fraction (LVEF) in a group of cancer patients with and without anthracycline therapy and/or radiotherapy involving the heart are reported.

**Material and methods**

Eighteen patients (17 females and 1 male, aged 30–74 years, median 47.5 years) who were referred to the department of nuclear medicine for a baseline cardiac assessment according to oncological protocols were included in the study (Table 1): 11 of these patients were investigated 11–228 months (median 60 months) after radiotherapy to the thorax, with or without adjuvant anthracycline-containing chemotherapy, while seven had received no previous cancer therapy (controls). Of the patients with cancer therapy, four had been treated with mantle field mediastinal irradiation for malignant lymphoma and seven with irradiation to the internal mammary lymph node chain for breast carcinoma with doses not exceeding 45 Gy; five patients had also received adjuvant anthracycline therapy with cumulative doses not exceeding 420 mg/m² epirubicin or 300 mg/m² doxorubicin. All controls were patients presenting with breast carcinoma. At the time of 123I-MIBG scintigraphy, all patients were free of cardiac complaints and none of them showed any evidence of ECG abnormalities. Excluding one cancer therapy patient (patient 6), who presented a period of peri-carditis 2 years after irradiation, none of the patients had previous episodes of cardiac disease or a history of hypertension. Another cancer therapy patient (patient 3) received treatment with Paclitaxel for cancer recurrence 8 months before radionuclide examination. Informed consent was obtained from all patients and the investigation protocol was approved by the ethical review committee of the hospital.

For 123I-MIBG scintigraphy, 185 MBq 123I-MIBG containing 0.2 mg MIBG (Cygne, Eindhoven, The Netherlands) was injected intravenously 60 min after thyroid blocking for the uptake of free 123I by oral administration of 200 mg potassium iodide. Cardiac 123I-MIBG parameters were determined according to a protocol described previously [10]. In short, the myocardial uptake of 123I-MIBG was quantified by a heart-to-mediastinum ratio (HMR) calculated by dividing averaged counts per pixel obtained from regions of interest on 10-min anterior planar images 4 h after 123I-MIBG administration, using a dual-head gamma camera (Vertex, ADAC). The myocardial washout of 123I-MIBG, calculated using cardiac regions of interest on left anterior oblique (LAO) planar images after 15 min and 4 h with a regular mediastinal region of interest for background subtraction, was determined according to the formula:

Myocardial washout = \( \frac{MC_{15 \text{ min}} - MC_{4 \text{ h}}}{MC_{15 \text{ min}}} \times 100\% \)

where MC=myocardial counts at 15 min and 4 h. Counts were corrected for 123I decay and normalized for injected dose. In addition, single-photon emission tomography (SPET) was performed to study regional distribution of the tracer in the myocardium. The parameters for SPET studies were 180° rotation, 60 s/frame, 32 frames, and reconstruction with Butterworth filter, cutoff 0.35. At the time of 123I-MIBG, none of the patients used drugs known or expected to interfere with MIBG uptake, such as tricyclic antidepressants, sympathomimetics and antihypertensive drugs, and they were asked to abstain from coffee or caffeine-containing beverages before and during the radionuclide study. LVEF was performed in the same week as 123I-MIBG scintigraphy on the basis of gated studies performed in the LAO position after administration of 740 MBq (20 mCi) of technetium-99m labelled human serum albumin, acquiring 30 frames per cardiac cycle. LVEF was measured using a semi-automatic processing with a varying region of interest.