

Late-onset cardiotoxicity of chemotherapy and radiotherapy

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ABSTRACT

An increasing number of patients with malignant lymphoma are becoming long-term survivors following treatment with chemotherapy (CT) and/or radiotherapy (RT).

Therefore, late therapy-related complications are becoming increasingly clear.

We present three young patients to illustrate the dire consequences of late-onset cardiotoxicity as sequel to potentially curative treatment.

We advise yearly life-long follow-up of CT/RT patients treated with curative intent.

Echocardiography should be performed when cardiac murmurs arise. Prevention of further cardiac damage by reducing other cardiac risk factors as well as endocarditis prophylaxis when indicated is recommended.

INTRODUCTION

With increasing successes in chemotherapy (CT) and/or radiotherapy (RT) many patients with malignant lymphomas have become long-term survivors of cancer. Therefore, an increasing number of potentially cured patients suffer from several therapy-related long-term effects, diminishing their quality of survival. We present three young patients successfully treated for their lymphoma to illustrate the impact of late-onset cardiotoxicity. We review the relevant literature and discuss possible guidelines to prevent potentially fatal cardiotoxic complications.

PATIENTS

Patient A

A 31-year old woman was diagnosed with large-cell anaplastic lymphoma stage IVb, localised in the right os ileum, para-aortic lymph nodes and subpleurally. She received eight cycles of CHOP chemotherapy (cyclophosphamide, adriamycin (cumulative dose 400 mg/m²) and prednisone) resulting in a partial remission. Subsequently she received two cycles of IMVP₁₆ (ifosphamide, methotrexate, VP₁₆), to which a complete remission was documented. Consolidation followed with high-dose chemotherapy according to the BAM schedule (BCNU, Ara C, melphalan) in combination with a G-CSF stimulated whole-blood stem cell transplant.¹ She was admitted to hospital three years later because of progressive dyspnoea of effort, palpitations and oedema for two weeks. Risk factors for coronary heart disease were smoking (10 cigarettes daily). On physical examination we saw a fatigued, breathless woman, with a blood pressure of 100/60 mmHg, arterial pulse of 112 beats/min. and an elevated central venous pressure. A holosystolic murmur was auscultated at the apex cordis as well as basal crackles over both lungs. An X-ray of the chest confirmed the diagnosis of congestive heart failure. The ECG showed sinus tachycardia without signs of ischaemia or myocardial infarction. Continuous electrocardiographic monitoring revealed short asymptomatic ventricular tachycardias. Laboratory examinations showed a pattern consistent with a small myocardial infarction. Echocardiography showed diminished left and right ventricular function, biatrial dilatation, and serious mitral and aortic regurgitation. She was treated with diuretics, an ACE inhibitor, digoxin and a β -blocker. Following discharge a strongly diminished exercise-tolerance persisted.

Additional workup showed a very high ferritin level (1115 µg/l) although HFE mutation analysis did not reveal the common genetic mutation for haemochromatosis.

Patient B

A 27-year old woman was diagnosed with nodular sclerosing Hodgkin's disease stage IIa, localised to left supraclavicular and mediastinal lymph nodes. Mantle field irradiation was given (4000 cGy in 20 fractions) to which she achieved a clinical complete remission. Six years later Hodgkin's disease recurred with localisations in mediastinal and right axillary lymph nodes. She was treated with MOPP/ABV chemotherapy (mitoxine, vincristine, procarbazine, prednisone/adriamycin (cumulative dose 215 mg/m²), bleomycin, vinblastine). After four cycles a clinical complete remission was attained which was consolidated with two additional cycles. During the next two years she developed hypothyroidism as well as premature onset of menopause. Five years after chemotherapy she was admitted to the hospital because of dyspnoea of effort, orthopnoea and palpitations. There were no risk factors for coronary heart disease. On physical examination the blood pressure was 150/80 mmHg, arterial pulse 120 beats/min and temperature was 37°C. A holosystolic murmur grade III/VI was found over the apex radiating to the left axilla, which had been absent previously. Crackles were heard over the left lung base. A chest X-ray showed bilateral pleural effusion, without signs of cardiac decompensation confirmed by spiral CT scan. Cytological examination of the pleural effusion showed polyclonal lymphocytosis without signs of lymphoma. All cultures remained negative. Pulmonary embolism was rendered unlikely by means of a normal ventilation-perfusion scan. Transoesophageal echocardiography showed a good systolic left ventricular function with marked mitral and aortic regurgitation, without valvular vegetations or papillary dysfunction, and some pericardial effusion. After treatment with diuretics her symptoms disappeared and never recurred. A tentative diagnosis of viral pleuropericarditis was made with possible diastolic myocardial dysfunction associated with valvular insufficiency, with a differential diagnosis of late-onset radiotherapy-induced pericarditis.² The knowledge of having developed a serious valvular insufficiency has made our patient's prospects for the future uncertain, as heart valve surgery will need to be considered if her valvular insufficiency worsens.

Patient C

A 35-year old woman was diagnosed with nodular sclerosing Hodgkin's disease stage IIa localised to left supraclavicular and mediastinal lymph nodes. She was initially treated with MOPP chemotherapy: after four cycles a complete remission was attained. As consolidation therapy mantle field irradiation was given. Three years later she developed hypothyroidism.

Six years after this combined modality treatment she was admitted to the coronary care unit because of chest pain irradiating to the left arm. Risk factors for coronary heart disease were smoking and a positive cardiovascular family history. On physical examination the blood pressure was 140/90 mmHg, arterial pulse 105 beats/min. On auscultation of the heart, a holosystolic murmur grade II/VI at the apex and a systolic murmur grade II/VI were noted at the left and right second intercostal space irradiating to the carotid arteries. The ECG showed sinus tachycardia with ST-segment depression in leads II, III, aVF as well as the precordial leads. After treatment with nitroglycerin the chest pain dissipated and the ECG normalised. Laboratory examination showed a troponin of 0.48 µg/l (normal < 0.2 µg/l), suggesting myocardial ischaemia. Transoesophageal echocardiography showed diminished left ventricular function and aortic regurgitation. Coronary angiography showed a significant stenosis of the ramus CX for which she underwent a PTCA with coronary stenting. This procedure had to be repeated four months later because of an in-stent stenosis. Three months after the second PTCA procedure an aortic valve replacement and coronary artery bypass grafting (aorta-Mo/Cx) were performed.

DISCUSSION

These three case histories illustrate the serious late cardiac sequelae of chemotherapy and radiotherapy that can occur even years after initial treatment. Anthracyclines, a group of potent chemotherapeutic agents widely used in the treatment of many different tumours, are known to cause acute and chronic cardiotoxicity.^{3,5} They cause a cumulative, dose-related, progressive, irreversible, and destructive cardiomyopathy. Pathological-anatomical examination shows dilatation of sarcoplasmic reticulum with disappearance of myofibrils finally culminating in myocardial fibrosis. The pathophysiology is thought to consist of binding of anthracycline metabolites to cellular iron, forming toxic free oxygen radicals that cause myocardial fibrosis.⁶ Acute cardiotoxicity can present as nonspecific ST/T-segment changes in the ECG, hypotension, tachycardias, arrhythmias and pericarditis during treatment with chemotherapy. Chronic cardiotoxicity presents as congestive heart failure, mostly (>80%) within one year after treatment, however in some cases even after a latency period of many years.^{7,8} The most widely used anthracycline is adriamycin (ADM). A cumulative dose of 400 mg/m² results in an incidence of heart failure of 0.4%, reaching 1 to 4% incidence at 500 mg/m², 7% incidence at 550 mg/m² and increasing to more than 20% at doses above 700 mg/m².⁹

Bolus infusions are more cardiotoxic than continuous infusions.¹⁰ Combining anthracyclines with high doses of cyclophosphamide or mediastinal irradiation can cause heart failure at lower cumulative doses.^{8,11} Known additional risk factors are very young and old age (>70 years), female gender and pre-existent cardiovascular disease.¹⁰ In our first patient we observed serious cardiomyopathy after a cumulative ADM dose of 400 mg/m². It is possible that pre-existent iron overload could have been a contributory factor.^{12,13} A general recommendation is to measure sequentially the left ventricular ejection fraction (LVEF) at rest by radionuclide angiocardiology (RAG) at different cumulative doses of ADM (0, 300, 450 mg/m² and every 50 mg/m² thereafter) and to stop ADM therapy when a significant reduction (>10%) and/or a subnormal value (LVEF <50%) is found.^{9,14,15} Additional RAG monitoring should be performed when continuous sinus tachycardia is observed without an evident cause and should be considered at a cumulative dose of 400 mg/m² when other cardiac risk factors are present. Subnormal baseline values (LVEF 30-50%) do not exclude ADM therapy provided that serial RAG monitoring is performed in these patients¹⁶ prompting cessation of anthracycline administration if the LVEF drops >10% and/or reaches a value <30%.

The value of RAG monitoring in the subgroup of patients less than 40 years of age receiving ADM up to a cumulative dose of 350 mg/m² has been questioned because heart injury in these patients nearly always remains subclinical.¹⁷⁻¹⁹ In addition, economic analysis has shown pretreatment RAG screening not to be cost-effective in this subgroup.²⁰

Moreover, it is questionable if RAG monitoring during treatment can predict late-onset cardiotoxicity as echocardiographic findings have been shown to worsen in the course of many years.²¹ Confounding this issue is the observation that only a modest agreement exists between echocardiographic methods and RAG.²² As our first patient demonstrates, congestive heart failure can occur unexpectedly after several years. Recently it was demonstrated that clinically manifest ADM cardiotoxicity can be predicted with good sensitivity early during treatment if the RAG ejection fraction drops 5% or more after receiving 200 mg/m² ADM.²³ This observation argues for continued use of baseline RAG monitoring but raises the issue whether RAG should be performed at this rather modest cumulative dose when administering potentially curative treatment. In the future, magnetic resonance imaging may provide a new tool in detecting anthracycline cardiotoxicity.²⁴ When treating lymphoma patients with curative intent, practical advice could be to monitor LVEF at baseline and at cumulative ADM doses of 300 mg/m² corresponding to

six cycles of CHOP therapy. A promising development in the prevention of anthracycline-induced cardiomyopathy is the cardioprotectant dexrazoxane (ICRF-187).²⁵ A meta-analysis of six randomised trials with disseminated breast cancer patients showed that the risk of developing clinical cardiotoxicity was significantly reduced when dexrazoxane was administered prior to ADM starting at a cumulative dose of 300 mg/m².²⁶ Whether dexrazoxane protects against late-onset cardiotoxicity has to be established. Randomised clinical trials have to be performed in lymphoma patients to establish if dexrazoxane can antagonise potentially fatal anthracycline-induced cardiomyopathy without loss of effectivity in potentially curative treatments. Anthracycline-induced congestive cardiomyopathy is treated with diuretics, digitalis, selective β -blockers and ACE inhibitors.²⁷ In younger patients heart transplants have been performed successfully.^{28,29}

Mediastinal irradiation is cardiotoxic as well. It can cause pericarditis, myocardial fibrosis and premature coronary heart disease.³⁰ The relative risk of cardiac death after mediastinal irradiation is increased threefold.^{31,32} Known additional risk factors are old age, pre-existent cardiovascular disease, female gender³³ and radiation dose (starting at 30 Gy). In about 25% of patients treated for Hodgkin's disease with mediastinal irradiation, a combined aortic and mitral valve regurgitation is found,¹¹ being caused by valvular fibrosis.³⁴ Two of our patients had such combined valvular disease. An important consequence for patients with valvular insufficiency is the need for endocarditis prophylaxis.

We conclude that it is increasingly clear that potentially curative cancer treatments can cause late-onset cardiac injury. In the long-term follow-up of potentially cured patients we advise evaluating cardiac function clinically at least every year to detect late-onset cardiotoxicity and to determine if endocarditis prophylaxis is necessary. The threshold for additional echocardiographic evaluation should be low. Prevention strategies to reduce other cardiac risk factors, such as high blood pressure, cholesterol, diabetes and smoking, seem indicated in these patients.

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