Strain and left ventricular volumes for predicting cardiotoxicity: a life-saving approach in anthracycline cancer treatment?

Jutta Bergler-Klein*

Department of Cardiology, Medical University of Vienna, Vienna, Austria

Online publish-ahead-of-print 23 July 2015

Introduction

Survival after cancer has greatly increased in the last decades, especially in patients with breast cancer, lymphomas, or after childhood cancer, due to advances in chemotherapy treatment regimens, as well as in surgical, radiation, and diagnostic imaging techniques. Therefore, potential side effects, especially those of the heart, play an increasing role for the long-term outcome of cancer patients with important public healthcare implications.

Cardiotoxicity of chemotherapy can occur acutely during or chronically with early onset after the therapeutic cycles, or with late onset even after many years and can be potentiated by radiation therapy. A multitude of antineoplastic agents are commonly complicated by the development of cardiotoxicity, including not only heart failure, but also myocardial ischaemia, hypertension, thromboembolism, arrhythmias with QT prolongation, or bradycardia.

Anthracyclines present an effective and life-saving cornerstone in cancer treatment. The expected 5- to 10-year survival rates of certain cancer entities, such as breast, haematologic, or childhood cancer currently already approach 80%, mainly due to the use of anthracycline derivatives, e.g. doxorubicin, but also to the development of modern targeted treatments. However, after many tumour-free years, 10–35% of patients may suffer from chronic, late cardiac sequelae such as latent or overt heart failure, especially in childhood cancer survivors or after breast cancer. The high cardiac morbidity of cancer survivors is frequently caused by the cumulative, dose-dependent irreversible myocyte necrosis caused by anthracyclines (Type I cardiotoxicity), and the addition of targeted receptor therapies that may alter the myocardial repair gene expression such as the monoclonal antibody trastuzumab in breast cancer (Type II cardiotoxicity). The cardiotoxic effects can persist and emerge clinically up to 30 years after the last cytostatic treatment or after radiation, and now represent the second most common cause of death after secondary or recurrent malignancy in cancer survivals.

Early diagnosis of cardiac dysfunction and prompt initiation of treatment is the key for at least partial recovery of left ventricular function and improved outcome. The time dependency in anthracycline-induced cardiomyopathy for possible achievement of improvement in LV ejection fraction by ACE-inhibitor and β-blocker heart failure therapy was established in several studies. Early non-invasive diagnosis of cardiac injury using echocardiography or multimodality imaging, and blood biomarkers such as natriuretic peptides (NT-proBNP, BNP) and/or troponines may point to the crucial early initiation of cardiac supportive treatment for the prevention of development of chemotherapy-induced cardiomyopathy.

In the present study, echocardiographic parameters of LV size and function for the prediction of cardiotoxic heart failure were examined in a large cohort of patients of undergoing anthracycline treatment for breast cancer (25%), blood cancer (57%), or other cancer types. Of 2208 patients, a group of 158 patients were identified with a borderline to low normal LV ejection fraction (EF) of 50–59% at baseline. Patients were followed for the occurrence of major adverse cardiac events (MACE). Importantly, MACE, all being congestive heart failure, occurred only in the group of EF 50–59%, although only few events were observed overall. The patients with heart failure development within a mean follow-up of 1.8 years were older (61 vs. 49 years), and more often had haematological cancer. The administered dose of anthracyclines was somewhat higher, but not significant, and no difference in radiotherapy application was observed. Cardiac risk factors were significantly more frequent, however, including diabetes and prior coronary artery disease in one-third of patients.

Importantly, baseline two-dimensional echocardiography identified simple, feasible parameters for the prediction of MACE. First of all, higher LV volumes, especially end-diastolic volume (LVEDV), were significant predictors of heart failure with a cut-off of > 61 mL/m² for indexed LVEDV. Intriguingly, MACE was significantly predicted by impaired global longitudinal LV peak systolic strain (GLS) averaged from the two-, three-, and four-chamber views; although in up to 13% of patients especially after left breast or chest surgery, the three-chamber view was not interpretable. However, LV EF did not play a role in this low–normal EF group. The observation that...
changes in EF are not reliably sensitive has been reported repeatedly also in valvular or other cardiovascular disorders and in the setting of chemotherapy. However, longitudinal strain has been shown to detect early and subtle deterioration of LV myocardial function. In the current study, impaired strain predicted a four-fold increase in MACE and a five-fold increase in symptomatic heart failure, independently of baseline EF. Follow-up echocardiography in patients developing MACE heart failure confirmed further deterioration of strain due to anthracycline chemotherapy.

Finally, overall mortality of the cancer patients was also significantly influenced by impaired global strain or LV EF. Although mortality was, of course, determined by cancer type and age, reduced GLS and EF in baseline echocardiography added important prognostic information. Myocardial dysfunction may also be a sequel of neuroendocrine effects of the tumour itself and by activation of inflammatory cytokines or immunologic pathways. On the other hand, patients with reduced LV function might perhaps be less prone to receive high-dose chemotherapy or radiation cycles.

Controversy exists about the standardization of the speckle tracking technology. However, the measurement of strain is easily performable in most patients, at least in two- and four-chamber views, and adds clinically relevant, non-invasive, serially repeatable prognostic information, which is underscored by the present study of cancer patients undergoing anthracycline chemotherapy.

Importantly, impaired myocardial strain at baseline should not preclude patients from receiving the life-saving chemo- or radiation therapy, but should lead to prompt and initiation of concomitant cardiac therapy for protection of further cardiotoxicity, e.g. from anthracyclines.

In summary, baseline impaired global longitudinal strain and increased LV volumes predicted heart failure MACE development in anthracycline therapy and even reflected overall mortality. Early treatment with heart failure medication is mandatory for optimal survival in cancer patients undergoing anthracycline or other chemotherapy.

Conflict of interest: None declared.

References