Review

The oncological treatment and cardiotoxicity problem – the role of biomarkers

Magdalena Dudek, Marta Kałużna-Oleksy, Jacek Migaj, Maciej Lesiak, Ewa Straburzyńska-Migaj

1st Department of Cardiology, Poznan University of Medical Sciences, Poland

Correspondence:
Magdalena Dudek
1st Department of Cardiology,
Poznan University of Medical Sciences, Poland
e-mail: magdalena.dudek@skpp.edu.pl

ABSTRACT

Cancer and cardiovascular diseases are a leading causes of morbidity and mortality in developed countries. Cardiological complications of oncological treatment are a significant problem that can be manifested in both permanent and transient cardiac dysfunction including myocardial damage, left ventricular dysfunction, and heart failure, hypertension, ischemia, as well as arrhythmias or QT prolongation, which can be life-threatening. Early detection of cardiotoxicity due to cancer treatment is crucial in the prevention of adverse cardiovascular outcomes in this group of patients. In this review we try to summarize the role of biomarkers in the detection of cardiotoxicity due to cancer treatment.
Key words: cardiotoxicity, biomarkers, cardiooncology, ST2, troponin

INTRODUCTION

Cancer and cardiovascular diseases are a leading causes of morbidity and mortality in developed countries. In the United States, these two diagnoses account for over 50% of the total number of deaths [1]. Cardiovascular diseases and cancer are one of the leading causes of mortality, also in Poland [2]. Early cancer detection, as well as the use of new treatment methods and the improvement of care, means that mortality in this group decreases, and the survival time of patients increases [2]. Anticancer therapies are associated with the risk of causing cardiovascular toxicity [3]. Long-term observation of cancer survivors show that the leading cause of death in this group are cardiovascular diseases [4]. Cardiological complications of oncological treatment are a significant problem that can be manifested in both permanent and transient cardiac dysfunction [5] including myocardial damage, left ventricular dysfunction (LVD), and heart failure (HF), hypertension, ischemia, as well as arrhythmias or QT prolongation, which can be life-threatening [6–8]. Disturbing cardiovascular symptoms may appear shortly after starting treatment, even on the same day or much later, even after several years [9]. Growing concerns about cardiotoxicity associated with the use of cancer therapy have led to the development of cardio-oncology. New methods are being sought to help predict adverse cardiovascular effects in cancer patients [8, 10].

BIOMARKERS

Early detection of cardiotoxicity due to cancer treatment is crucial in the prevention of adverse cardiovascular outcomes in this group of patients. Currently, available data suggest that cardiotoxicity, detected at an early stage, is potentially reversible [11, 12]. The most common strategies for assessing the risk of cardiotoxicity, as a complication of oncological treatment, are an echocardiographic assessment of left ventricle ejection fraction (LVEF) or less frequently multigated acquisition scan (MUGA scan). Identifying patients with subclinical cardiac dysfunction who are at risk of developing heart failure, by using cardiac biomarkers, may be crucial for matching the right therapy and minimize the development of cancer treatment-induced cardiotoxicity. What is more, cardiac biomarkers may be useful in this group of patients for adjusting personalized oncological treatment and rapid implementation of cardioprotection. In 2016 European Society of Cardiology (ESC) published a position paper regarding the management of the cardiotoxicity developed after oncological treatment [8]. A year later, the American Society of Clinical Oncology published similar guidelines [13]. According to that documents, cardiac biomarkers, such as troponin and natriuretic peptides, may be considered as an additive tool in diagnosing myocardial damage.

Troponin is one of the most established cardiac biomarkers for acute coronary syndrome and is routinely measured in acute myocardial infarction and has diagnostic and prognostic value [12]. Troponin is a sensitive and specific marker of myocardial injury and, apart from an acute coronary syndrome, may be elevated in case of heart failure, arrhythmia, pulmonary embolism and may be present in patients with cancer. The association of elevated troponin I (TnI) levels in cancer patients with cardiotoxicity has been investigated in several studies. Newly elevated TnI may identify patients form a group with poor prognosis [14]. The new elevation of high sensitivity troponin I can predict cardiotoxicity occurrence in patients treated with doxorubicin and/or trastuzumab [15]. Kitayama et al. obtained similar results that elevated levels of high sensitive troponin T in breast cancer patients can also predict the occurrence of cardiotoxicity [16].

Natriuretic peptides, N-terminal pro brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP), are secreted from the cardiac ventricles as a response to increased wall tension may be used as a biomarker [17]. NT-proBNP is a well-established biomarker for the diagnosis of heart failure and is associated with prognosis in HF patients. A recent study showed that NT-proBNP increases during trastuzumab treatment and is correlated with LVEF [18], which is consistent with previous findings [19]. Romano et al. showed that measurements of NT-proBNP might be useful for early detection of cardiotoxicity in patients receiving anthracyclines [18]. The cardiotoxicity related to anthracycline therapy also may be detected by using BNP [20].

Many other biomarkers are currently being studied and may have potential utility in the detection of early cardiotoxicity and outcome prediction. In a recent publication, Canada et al. showed that elevated levels of C-reactive protein (CRP) are common in a group of patients receiving chest radiotherapy [21]. They found a correlation between CRP levels and LVEF, which was lower in a group with elevated CRP. The results of this study suggest that changes in CRP levels may be useful for outcome prediction in patients receiving radiotherapy, however due to small sample size, further research in this field is needed.

Myeloperoxidase (MPO), an enzyme released by neutrophils, in periods of inflammatory stress and is considered as a biomarker of cardiotoxicity. Oxidative stress is thought to be one of the causes of cardiotoxicity caused by doxorubicin and trastuzumab. Ky et al. study suggest that MPO can be an adjunct biomarker to troponin [15]. Increased MPO levels are associated with cardiotoxicity over the entire course of doxorubicin and trastuzumab therapy [22]. These findings are encouraging for further studies in this field.

Soluble ST2 (sST2) is a promising biomarker being investigated in many fields of cardiology [23]. ST2 participates in inflammatory processes and functions in relation to immune diseases. What is more, ST2 with interleukin-33, takes part in the cardioprotective pathway that prevents fibrosis and inhibits the inflammatory response, hypertrophy, and apoptosis of cardiomyocytes. sST2 as a novel biomarker seems to be especially important for monitoring acute and chronic HF [24, 25]. Considering the release mechanism of sST2 and its usefulness in the assessment of patients with heart failure, it appear that determination of sST2 may be useful in patients with cardiotoxicity after oncological treatment.

SUMMARY

Drug administration in the prevention of cardiotoxicity is the subject of ongoing research. ESC advise treatment with ACE inhibitor when an absolute LVEF decline of > 10% [8]. Administration cardiac medications for the prevention of cardiotoxicity in patients with normal cardiac function and low risk before oncological treatment needs more research to be done. However, there is promising meta-analysis endorsing preventive drug administration [26]. Treatment with dexrazoxane, β-blocker, statin or angiotensin antagonists may play a role in reducing cardiotoxicity [26]. A recent publication shows that ramipril treatment exerts potentially protective effects on cardiotoxicity [27].

The potential impact of cancer therapy on the cardiovascular system becomes a challenge for oncologists and cardiologists. The goal is to find a balance between oncological therapy, often life-saving, and the possibility of cardiotoxic side effects that reduce the quality of life and shorten its duration. Given the limitations of currently available biomarkers an approach based on the simultaneous assessment of multiple markers is recommended.

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