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Cardiotoxicity: Importance of biomarkers

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Abstract

The clinical efficacy of chemotherapy, as a recognized therapeutic approach for malignant diseases, usually has certain limitations due to its cardiotoxicity (CT) and consequent cardiomyopathy, or even heart failure. CT is defined as any cardiac injury connected with oncology treatment, whether it is chemo-, radio-, targeted or immunotherapy, or cancer by itself, and it represents a great challenge for clinicians in everyday practice. A wide spectrum of factors related to chemotherapy (type of drug, dose during each cycle, cumulative dose, schedule, method of application, combination with other cardiotoxic drugs or association with radiotherapy) and patient characteristics (age, presence of cardiovascular risk factors, previous cardiovascular disease) are the determining factors that influence the frequency of CT. Imaging methods for morphological and functional monitoring of the heart muscle are used for monitoring CT. The quest for diagnostic tools for early CT detection is of great significance. In line with this, the measurement of some cardiac biomarkers has found its place in clinical settings as an early determinant of myocardial injury. Therefore, in this review article, special attention will be paid to certain well-established, as well as certain novel cardiac biomarkers, and their role in recognizing asymptomatic CT, in order to gain deeper insight into their diagnostic utility.

Keywords: cardiotoxicity biomarkers, anthracyclines, trastuzumab

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Introduction

The term "cardiotoxicity" was first mentioned in 1946 to describe cardiac toxicity caused by mercury, digitalis preparations, and local anesthetics. In the 1970s, this term began to be used to describe complications at the heart level during the administration of anthracyclines, adriamycin, and 5-fluorouracil. Although cardiotoxicity is mainly associated with the use of oncology therapy, it can also be caused by the use of other drugs (1, 2). The definition of cardiotoxicity (CT) introduced by the European Society of Cardiology (ESC) is “any structural or functional cardiac injury connected with oncology treatment, refer[ring] to radiotherapy, chemotherapy and cancer itself”(3). The National Cancer Institute (NCI) defines cardiotoxicity in very general terms as "toxicity affecting the heart" (4).

Types of cardiotoxicities

There are several divisions of CT, but two basic divisions are generally used in clinical practice, based on the time of manifestation and the mechanism of occurrence. In relation to the time of manifestation, cardiotoxicity can develop as acute, subacute or chronic. Acute CT is characterized by the occurrence of cardiac function impairment from the moment of application of the therapy until 2 weeks after discontinuation of oncology treatment. Most often, these phenomena are abnormalities in ventricular repolarization, changes in the QT interval, supraventricular and ventricular arrhythmias, acute coronary syndrome, pericarditis and myocarditis. Acute CT is rare, unrelated to dose, and most commonly associated with preexisting heart disease. Subacute CT is a newer clinical entity that is not precisely defined. It is rare and appears up to 4 weeks after the application of chemotherapy. It manifests itself most often as cardiac edema and reversible left ventricular myocardial dysfunction. Chronic or late CT is best studied with anthracyclines in clinical practice. It is divided into subgroups, one where symptoms can occur one year after oncology treatment, and another subgroup where symptoms can occur later, after more than one year from the application of chemotherapy. The most common sign of chronic CT is left ventricular (LV) systolic dysfunction (predominantly asymptomatic), which can lead to severe congestive heart failure over time (5).

Considering the mechanism of CT occurrence, two types may be distinguished: type I and type II. Type I CT is most investigated on anthracyclines and is associated with increased cardiovascular mortality. Irreversible changes can be seen electromicroscopically as sarcomere damage and necrosis. Type II CT is most thoroughly investigated on the example of monoclonal antibodies-trastuzumab. Changes that were recorded on pathohistological specimens of endomyocardial biopsies were ultrastructural and reversible. This type of cardiotoxicity was not correlated with increased mortality of cardiovascular disease. Risk factors for higher cardiotoxicity became more prominent as a consequence of chemotherapy. The frequency of CT depends on various factors regarding chemotherapy (type of drug, dose during each cycle, cumulative dose, schedule, etc., method of application, combination with other cardiotoxic drugs or

association with radiotherapy) and patient characteristics (age, genetic predisposition, presence of cardiovascular risk factors, previous cardiovascular disease) (6, 6a).

Monitoring cardiotoxicity

There are several ways of monitoring CT. One of them are imaging methods for morphological and functional monitoring of the heart muscle, and the other is related to serum biomarkers. Another method, biomarkers - blood particles, can be very useful in the management of cancer patients who are receiving cardiotoxic oncology treatment. The goal of biomarkers is to detect potential CT events before cardiac muscle injury and before clinical symptoms and signs of heart failure (HF) are developed (7, 8). In 2016, the ESC Guidelines defined HF grounded on the left ventricular ejection fraction (LVEF) into ejection fraction (EF) >50%, mid-range EF (40–49%) and reduced EF (<40%) (9). The European Society of Medical Oncologists (ESMO) and Common Terminology Criteria for Adverse Events (CTCAE) definition of heart failure (HF) depends on the symptoms and LVEF decrease. The cut off LVEF is 55%. In symptomatic HF, EF decreases by 5% or more, while in an asymptomatic HF EF decreases by 10% or more (10).

The single use of biomarkers is not sufficient to detect the potential for the development of CT. Therefore, the use of other methods, primarily imaging methods for the detection of CT, are of utmost importance. When both are used, biomarkers and imaging methods enable the prediction of early possibility for CT development, and prevention, monitoring and treatment of CT in the future (8). In that sense, the collaboration of oncologist and cardiologists is of paramount importance. The main challenge is related to the search for biomarkers that should be used and determining which patients should be monitored, as well as when and how often specific biochemical tests and/or clinical examinations should be ordered in order to provide better recognition and management of cardiooncology toxicity.

If we want to detect early cardiac, especially left ventricular (LV) dysfunction or injury where imaging strategies are contiguous, and not showing cardiac disabilities, biomarkers can be used to detect the earliest heart modifications, and even to predict the possibility of heart failure development. Biomarkers of CT can be measured at baseline, during oncology treatment, and when the treatment is finished, as follow-up biomarkers. The main purpose of implementing CT biomarkers is the monitoring and managing of cardiac adverse events during and after oncology treatment (7).

Cardiotoxicity caused by different therapies

The greatest impact on HF is made by anthracyclines and a few target therapies. Immunotherapy seems very safe, according to present investigations and experience. Preventing, treating and recognizing HF is the most important aim.

Cardiovascular toxicity (CVT) was first explained in anthracycline treatment and radiation therapy (RT). New oncology treatments, such as multi-targeted tyrosine kinase inhibitors (TKI) and vascular endothelial growth factor (VEGF) inhibitors, can also cause

CVT. Left ventricular dysfunction is mostly caused by anthracycline treatment, while radiation therapy is related to valvular dysfunction and coronary artery disease. TKI and VEGF often cause arrhythmias, QT prolongation and pulmonary hypertension (Figure 1) (11, 12).

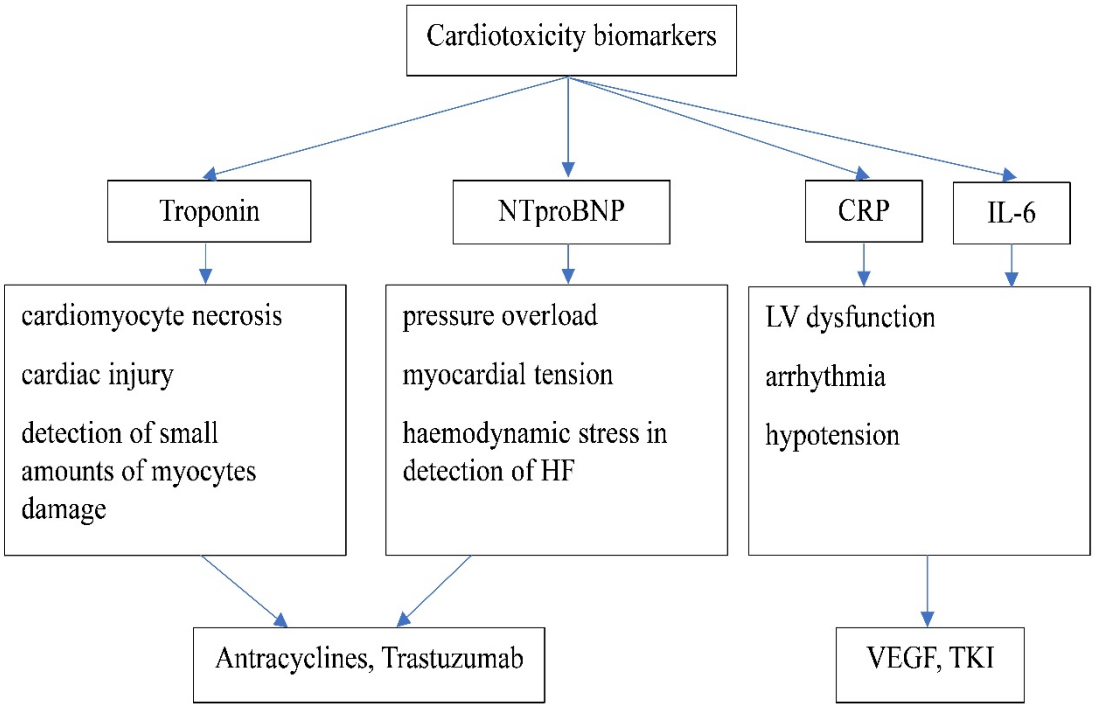

Figure 1. Cardiotoxicity biomarkers and their specificity

Slika 1. Biomarkeri kardiotoksičnosti i njihove specifičnosti

Cardiotoxicity biomarkers and their specifications will be explained further in the article. Some of them, e.g., anthracyclines, are recorded during the treatment, and some of them are discovered 12 months after the treatment, while some are even found 20-30 years later (13).

Trastuzumab is a monoclonal antibody generated against the HER2/Neu receptor that may cause left ventricular dysfunction, which in severe cases can lead to HF (14, 15). Trastuzumab firstly causes functional changes, but if it is applied after the anthracyclines which have initiated myocyte necrosis or apoptosis, it may aggravate the cardiac injury and cardiomyocyte cell death.

Immune checkpoint inhibitors (ICIs) destroy cancer cell by activating the immune system. Those are programmed cell death protein-1 (PD-1), programmed cell death protein ligand-1 (PD-L1), cytotoxic T lymphocyte–associated protein 4 receptor

(CTLA4) and chimeric antigen receptor therapy (CAR-T therapy). ICIs can be the cause of some cardiotoxic events, such as acute coronary syndromes, pericarditis, myocarditis, atherosclerotic rupture of plaque, complete heart block, immune-mediated, autoimmune vasculitis. Therefore, ICIs are shown to be significant biomarkers of CT (16). Concerning the above mentioned, biomarkers for this broad range of CV unwanted effects need to be developed for a more profound approach.

Diagnostic methodology of Cardiotoxicity

One of the most convenient options for detecting cardiotoxicity is echocardiography. Cardiotoxicity is defined as a decrease in LVEF > 10% below the normal value of ejection fraction (3). The frequency of imaging diagnosis of cardiotoxicity is planned based on the baseline cardiovascular status, type of oncology treatment, dosage, administration regimen, and adverse events. The main purpose of detecting CT is the evaluation of myocardial damage before symptoms occur and declining EF in cases where myocyte injury is not reversible.

Cardiac Troponin

Cardiac troponins (cTn I and T) are sensitive parameters for the recognition of cardiomyocyte necrosis and cardiac injury. Their most common use is in acute coronary syndrome (ACS) and its elevation is a prognosis-predictor in acute myocardial infarction (MI) (5, 17, 18). As anthracyclines may injure the cardiac muscle and lead to necrosis, the levels of troponin, preferably I that T, may be elevated (14). Troponins exhibit high specificity for cardiac injury, with the detection of small amounts of damage of myocytes. Troponins enable providing therapy to minimize CT prior to the occurrence of irreversible LV dysfunction. Higher troponin concentrations correlated with a greater level of LVEF reduction and cardiac injury in comparison with transitory elevations in the values of troponin (19). Cardiac troponin elevation was detected in 21–40% of patients after anthracycline chemotherapy, both cTn I and T. Cardiac troponin elevations are comparable with the dosage of anthracyclines, as well as with myocardial damage. In some trials, representative levels ranged from 11 to 120 ng/L in low-dose, and 160 to more than 1900 ng/L in high-dose anthracycline regimens (14). Recently, Cardinale et al. (18) have concluded that cTns might be a severity predictor factor after anthracycline treatment because of their close correlation with LVEF reduction. Cardiac troponins may be taken as myocardial risk verification after chemotherapy, where the evaluation of personalized frequency of cardiac monitoring should be estimated. On the other hand, having insight into the potential cardiotoxicity may enable providing cardioprotective therapy (18, 19, 20, 21, 22).

ANTHRACYCLINES

Clinical studies have concluded that higher troponin levels are detected during anthracycline administration in both adult and children chemotherapy. They represent an early indicator of increased risk of LV dysfunction (14, 19). Data have shown that worse cardiac impairment and higher reduction in LVEF correlates with higher levels of

troponin. It has also been shown that troponin is a sensitive cardiotoxicity biomarker, and most importantly, that cTns correlates with imaging methods that predict HF (23-25).

TRASTUZUMAB (Herceptin)

The treatment for HER2+ breast cancer with HER2+ agents can harm cardiac function reversibly. Some trials have confirmed that patients who developed LV dysfunction rapidly recovered cardiac function after the interruption of treatment. Some of them did not have high values of troponin (20). In the largest trial where troponin concentration was measured, the HERA trial, it was concluded that troponin was elevated after anthracycline, but before trastuzumab.

Immunotherapy

Immune checkpoint inhibitor (ICI) most often causes myocarditis, and therefore elevated troponin values (26). ICI-mediated myocarditis is preferably diagnosed by troponin elevation. Mahmood et al. (26) recorded that patients who had been discharged with elevated troponin values had higher risk for major adverse cardiac events (MACE). In order to detect ICI myocarditis, it is suggested that troponin measurement should be provided at baseline and regularly up to the third cycle (27, 28).

Natriuretic Peptides

Cardiomyocytes produce two natriuretic peptides (NP), brain natriuretic peptide (BNP) and N-terminal pro-B type natriuretic peptide (NT-proBNP). Natriuretic peptides are important biomarkers of pressure overload, myocardial tension and haemodynamic stress in the detection of HF (23, 24, 25, 29, 30, 31). This is why NPs are important cardiotoxicity biomarkers of HF. Natriuretic peptides may be increased within 24h hours from anthracycline chemotherapy in order to recognize acute CT (32, 33). Natriuretic peptides measuring is important not only for detecting CT, but also for recognizing the level of cardiac dysfunction. It appears that BNP measurement is as important as imaging methods in detecting CT. In the HERA study, the elevation of NT-proBNP during the treatment with trastuzumab was shown to be the best predictor of LV dysfunction on echocardiography monitoring. Natriuretic peptides are increased in patients with ICI-mediated myocarditis (28). Elevated levels of NPs are detected in elderly female patients, as well as in renal dysfunction and in cancer-related inflammation (34-36).

Inflammatory Mediators

Interleukin -6 (IL-6), C-reactive protein (CRP) and high-sensitive CRP (hsCRP) are inflammatory biomarkers related to elevated risk of cancer and cardiovascular events (37). The elevation of hsCRP is in positive correlation with HF and manifesting LVEF decreasing (38). In the study of Onitilo et al., a total of 54 women were treated with trastuzumab. Results showed that hsCRP higher than 3 mg/L showed a 92.9% sensitivity and 45.7% specificity for the reduction in LVEF (39). The highest values of hsCRP were recorded after a median of 2.5 months before cardiotoxicity, and they were manifested by

imaging quantification in LVEF decrease. On the contrary, other studies did not show the correlation between a rise in CRP level and CT (40). The importance of CRP measurement can be recognized in cytokine release storm, characterized by LV dysfunction, arrhythmia, hypotension and cardiac arrest (41, 42).

Kotur-Stevuljevic et al. (43) reported that the development of oxidative stress is one of the mechanisms of action of chemotherapeutics, and there is an expectation that they will also affect the heart. According to that, oxidative stress is probably one of the mechanisms of heart damage during chemotherapy. Oxidative stress status markers (malondialdehyde (MDA), superoxide anion (O2), and markers of inflammation (fibrinogen and hs CRP), have a positive correlation in coronary artery disease (CAD) patients. Antioxidant enzyme superoxide dismutase (SOD) activity was in a negative correlation with hsCRP concentration. Oxidative stress is an important pathway for coronary artery disease (CAD) formation. Oxidative stress status markers have no impact on the extent of CAD. For one of inflammatory markers, hsCRP, it was concluded that it has a correlation with CAD severity (44).

New Cardio-Oncology Biomarkers

Cardiac biomarker monitoring - before, during and after the application of oncology therapy, was created due to an immense need for understanding the mechanisms of CT induced by chemotherapeutics. In this regard, new biomarkers have been developed over the last years and decades, with the goal not only to assess who has already developed, but also who will potentially develop CT, and to estimate its level.

Myeloperoxidase (MPO)

Myeloperoxidase (MPO) is an enzyme produced by polymorphonuclear leukocytes (45). It has a pro-atherogenic and pro-oxidant influence on the cardiac muscle (46). Its increase is in correlation with higher risk of CAD and acute HF and it can therefore be named as a predictive biomarker of poor ACS and acute HF prognosis (45, 47, 48). Higher MPO values based on oxidative stress are recognized in patients with anthracycline and trastuzumab treatment (49). Ky and al., in a trial with doxorubicin and trastuzumab treatment, concluded that MPO levels were clinically significant even at baseline (a characteristic unique to this biomarker ($p = 0.052$)), and also clinically significant in terms of the absolute difference in its levels between the second cycle compared to the one at baseline (HR 1.34; 95%CI, 1–1.8; $p = 0.048$) (41).

Endotelin-1

Endothelin-1 (E-1) is a blood vessel protein which has a huge impact on the pulmonary and cardiovascular system. It is well known as a blood vessels constrictor, but also with extravascular effects, proliferation and remodeling of smooth muscle cells, an increase of lipid deposits in the wall of blood vessel, and possible coronary thrombosis. All the mentioned mechanisms create injuries to coronary arteries, deteriorate myocardial perfusion and contribute to heart failure. Elevated E-1 and heart failure occurs more

frequently in patients with breast cancer who were treated with Her2 monoclonal antibodies, alone or in combination with an anthracycline (50).

Biomarkers of myocardial fibrosis

Myocardial fibrosis is a key of cardiac remodeling that leads to heart failure and death. Enhanced myofibroblastosis and excessive extracellular matrix deposition are the results of myocardial fibrosis. Myocardial fibrosis might be detected by serum biomarkers, cardiac magnetic resonance imaging, and endomyocardial biopsy (51). In addition, some of the myocardial fibrosis biomarkers related to oncology treatment will be explained.

Galectin-3 is a multifunctional lectin produced by macrophages and involved in a lot of biological processes, both physiological and pathophysiological. It is recognized as a biomarker connected with macrophage activation, production of proinflammatory cytokines, induction of oxidative stress, apoptosis (52, 53), chronic inflammation, tissue fibrosis and remodeling (41, 54). Galectin-3 activity is based on the stimulation of the pro-fibrotic path that leads to fibroblast proliferation and collagen storage (41). Targeting cardiac tissue, higher values of galectin-3 might be detected and related to acute/chronic decompensated HF (55, 56). In patients with either acute or chronic decompensated HF, studies have shown that galectin-3 levels are important in predicting mortality rates (55, 57). Higher values of galectin-3 are documented in atherosclerosis, ACS, HF, but also in COPD, kidney disease. Moreover, other factors such as age, female sex, kidney function, obesity and diabetes can impact galectin-3 values (58).

Growth differentiation factor-15 (GDF-15) is associated with oxidative stress, inflammation, tissue injury in oncology, diabetes, renal and pulmonary patients. GDF-15 levels have detected atherosclerosis and HF and indicated their severity (58, 59, 60, 61).

MicroRNAs (Non-coding RNAs)

MiRNAs (Non-coding RNAs) play a significant role in almost all metabolic processes. They include cell differentiation, replication, regeneration and apoptosis. miRNAs are recognized in a number of physiological and pathological processes, like epithelium differentiation, normal granulocyte development, inflammation, infections, apoptosis, fibrosis, other immune-mediated disorders, including allergy, and cancerogenesis (62). They are stable and can be analyzed in plasma, serum (63, 64), urine (65) and saliva (66). In addition, miRNA levels can be detected by different sensitive techniques, such as quantitative real-time PCR (RT-qPCR) and next-generation sequencing. In 2008 circulating miRNAs were described, and their importance became even greater. Circulating miRNAs have their origin in different tissues and may enter the plasma after tissue transformation, specified stimulus or cell death. According to miRNA tissue specificity, the provenience of precise circulating miRNAs can be recognized and used as a biomarker for numerous tissue injuries and diseases, such as allergies, asthma and autoimmunity (67). Moreover, miRNAs are acknowledged as toxicological, drug induced biomarkers for safety assessment and tissue injury. Early releasing and miRNA

tissue specification, when the injury is reversible, are the most valuable benefits in toxicology. Towards the assessment of drug safety, miRNAs were found to correlate with cardiotoxicity, hepatotoxicity and nephrotoxicity (68, 69, 70). This review article is focused on miRNA utilization in drug-induced cardiotoxicity. Ruggeri et al. have concluded that MiRNA elevations are connected with myocardial tissue injury and different cardiovascular diseases (myocardial infarction, acute coronary syndrome, acute heart failure, cardiac hypertrophy, essential hypertension and atherosclerosis) (71, 72, 73). In that way, miRNAs have an important role in myocardial pathogenesis, both in diagnostic and prevention. Changes in the levels of certain miRNAs in the heart and/or plasma have been reported in cases of atherosclerosis, hypertension, ACS, MI, HF and cardiomyopathy (CMP) (74). The high content of miR-a, miR-133, miR208a/b and miR-449 in myocardial tissue speaks in favor of their cardio-specificity and make them possible cardiac biomarkers (75). In addition, miRNAs are elevated even if there is low cardiac cell injury and low toxin concentration. This is a valuable preference compared to other, not as sensitive biomarkers (76, 77). The cardiospecificity of miRNA is very valuable and indicates that miRNA could be a biomarker of very early myocardial damage induced by a drug or by another pathology. In that way, miRNA elevation can be used in prevention, but also in the detection and improvement of drug-induced cardiotoxicity (67). The elevation of circulating miRNA could be a valuable early CT biomarker of DOX induced cardiotoxicity, as shown in miR 1, miR 133a and iRm 208 levels (78, 79).

Genome-wide association studies (GWAS) are investigated in pharmacogenomic trials where genetic drivers, mostly (a) single nucleotide polymorphisms (SNP) or (b) genome-wide association studies (GWAS) are investigated and connected to a specific phenotype. Trials investigate genes from one SNP to a complete gene sequence, while GWAS analyzes several hundred thousand to millions of SNPs. Trials based on GWAS have been on the increase in the last years (80). One of the major GWAS trials was conducted in Japan (NCCTG N9831 trial), with HER2-positive breast cancer treated with anthracyclines and then paclitaxel ± trastuzumab. The main aim of the trial was to recognize a novel genetic marker (or markers) determining the risk of trastuzumab-induced cardiotoxicity. It identified five independent loci showing a possible association with trastuzumab-induced cardiotoxicity. According to this, a predictive value for trastuzumab-induced cardiotoxicity was developed using the five marker SNPs (rs9316695, rs28415722d, rs7406710, rs11932853 and rs8032978) (81).

Proteomics and metabolomics are specific methods used for the determination of many, if not all, proteins and metabolites in one cellular/tissue compartment or in one sample type, which are used for disease diagnosis improvement (82). The aim is to investigate the initial mechanism of DOX-induced CT in order to discover, prevent and treat CT. Cheng et al. investigated the discrepancies of metabolites and proteins during DOX-induced HF in rats, explained the mechanism of heart failure at the phenotypic and genotypic levels, and provided a reference for the study of DOX-induced heart failure (83).

Conclusion

In cardio-oncology, cardiotoxicity is defined as any cardiac injury connected with oncology treatment. Except imaging methods, there are also recognized serum biomarkers as very useful diagnostic tools for the detection of CT. Cardiac troponins, miRNA and MPO have recognized biomarkers for acute CT. NTproBNP, GWAS, GDF15, galectin-3 may point to both acute and chronic CT. The discovery of biomarkers with significant predictive potential for early asymptomatic CT is the main goal of future investigations, which should enable better myocardial tissue protection.

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Kardiotoksičnost: Važnost biomarkera

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Kratak sadržaj

Klinička efikasnost hemioterapije, kao priznatog terapeutskog pristupa malignim bolestima, obično ima određena ograničenja zbog svoje kardiotoksičnosti (KT), te posledične kardiomiopatije, pa čak i srčane insuficijencije. KT se definiše kao svaka povreda miokarda povezana s lečenjem raka, uzimajući u obzir hemioterapiju, radioterapiju, biološku ili imunoterapiju, kao i sam karcinom, te predstavlja veliki izazov za kliničare u svakodnevnoj praksi. Širok spektar faktora povezanih s hemioterapijom (vrsta leka, doza tokom svakog ciklusa, kumulativna doza, raspored, način primene, kombinacija s drugim kardiotoksičnim lekovima ili povezanost s radioterapijom) i karakteristike bolesnika (dob, prisutnost faktora kardiovaskularnog rizika, prethodne kardiovaskularne bolesti), odlučujući su faktori koji utiču na učestalost KT. Za praćenje KT koriste se radiološke metode za morfološko i funkcionalno praćenje srčanog mišića. Potraga za dijagnostičkim alatima za rano otkrivanje KT od velikog je značaja. U skladu s tim, merenje nekih srčanih biomarkera kao rane determinante povrede miokarda našlo je svoje mesto u kliničkim okruženjima. Stoga će u ovom preglednom članku posebna pažnja biti posvećena nekim dobro utvrđenim, kao i nekim novim srčanim biomarkerima, i njihovoj ulozi u prepoznavanju asimptomatske KT, kako bi se stekao dublji uvid u njihovu dijagnostičku korisnost i neželjene efekte lekova koji se primenjuju u terapiji karcinoma.

Ključne reči: biomarkeri kardiotoksičnosti, antraciklini, trastuzumab

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