Razvoj definicije i reinterpretacija kardiovaskularne toksičnosti

The evolution of defining and the reinterpretation of cardiotoxicity

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SAŽETAK: Jedno od vodećih načela kardioonkološke prakse jest minimiziranje nepotrebnog prekidanja antitumorskog liječenja. Glavni je cilj ove specijalizacije osigurati da bolesnici s karcinomom dobiju najbolju moguću terapiju na siguran način, a pri tome na najmanju moguću mjeru svesti kardiovaskularnu toksičnost povezanu s onkološkom terapijom (CTR-CVT) tijekom skrbi. U ovom su radu opisane prethodne i trenutačne definicije CTR-CVT-a i ukratko predočeni ključni *CARDIOTOX* registar te odgovarajući dijelovi nedavno objavljenih prvih kardioonkoloških smjernica Europskoga kardiološkog društva. U radu nastojimo dati uvid u aspekte precizne medicine povezane s kardioonkologijom.

SUMMARY: One of the guiding principles of cardio-oncology practice is to minimize the unnecessary interruption of antineoplastic therapy. The overall goal of the specialty is to ensure that cancer patients receive the best possible anticancer therapy safely, while minimizing cancer therapy-related cardiovascular toxicity (CTR-CVT) during oncology care. In this paper, we describe prior and current definitions of CTR-CVT and briefly present the landmark CARDIOTOX registry, as well as corresponding parts of the recently published, first cardio-oncology guideline of the European Society of Cardiology. In our paper, we aim to provide insight into the cardio-oncology-related aspects of precision medicine.

KLJUČNE RIJEČI: kardioonkologija, kardiotoksičnost, antitumorsko liječenje, CARDIOTOX registar.

KEYWORDS: cardio-oncology, cardiotoxicity, anticancer treatment, CARDIOTOX registry.

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Uvod

Kardioonkologija je multidisciplinarno područje koje postoji nešto više od dva desetljeća i još uvijek je relativno novo. Posljednjih su godina promjene u epidemiologiji i vodećim uzrocima smrti dovele do novih znanstvenih spoznaja o kardiovaskularnim (KV) i onkološkim bolestima[1]. Uočeno je da se dvije skupine bolesti znatno preklapaju ne samo s obzirom na čimbenike rizika i patomehanizme nego i druga svojstva međusobna djelovanja kroz složene mehanizme signaliziranja. Stoga nije neuobičajeno da se u istog bolesnika pojave oba stanja. Osim gore navedenih razloga, taj se fenomen djelomično može objasniti činjenicom da mnoge različite vrste onkoloških postupaka potencijalno mogu izazvati KV nuspojave, poznate pod nazivom kardiotoksične nuspojave. Stoga nije slučajno da je kardiotoksičnost uzrokovana antitumorskim liječenjem jedno od glavnih pitanja u kardioonko-

Introduction

Cardio-oncology is a frontier discipline that has existed for more than 2 decades, yet it is still a relatively young field. In recent years, changes in the epidemiology and leading causes of death have brought new scientific findings on cardiovascular and oncological diseases to focus[1]. It has been recognised that the two groups of diseases have a significant overlap not only in their risk factors and pathomechanisms, but also in their other interplaying properties through complex signalling mechanisms. For these reasons, it is not uncommon for the two conditions to present in the same patient. In addition to the reasons listed above, this phenomenon is also partly explained by the fact that many different types of oncological treatments have the potential to induce cardiovascular adverse effects, classically known as cardiotoxic side effects. Thus, it is no coincidence that cardiotoxicity caused by

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logiji. Zbog tih nuspojava onkološka terapija može biti manje uspješna, a može se također skratiti očekivani životni vijek i kvaliteta života bolesnika oboljelih od karcinoma. Ovom je pitanju posvećeno nekoliko preporuka, izjava i konsenzusnih dokumenata s različitim definicijama kardiotoksičnosti[2-6]. Precizna i točna definicija kardiotoksičnosti nije važna samo radi nomenklature već je i važan čimbenik pri donošenju odluke o daljnjem liječenju onkoloških bolesnika. Upravo je zbog toga važno odrediti kardiotoksičnost, a takva dijagnoza može dovesti do privremene obustave ili čak trajnoga prekida onkološke terapije. Rane definicije kardiotoksičnosti usredotočile su se na klasičnu kardijalnu disfunkciju povezanu s terapijom karcinoma (CTRCD) kao glavnu komponentu nuspojava i podijelile su kardiotoksičnost na dva osnovna tipa: kardiotoksičnost tipa I. uzrokovanu antraciklinima, koja se prije smatrala ireverzibilnom, ali se danas smatra reverzibilnom, i kardiotoksičnost tipa II. uzrokovanu trastuzumabom koji se, u pravilu, smatra reverzibilnim[7]. S obzirom na nedavna postignuća u znanosti i pojavu novijih onkoterapijskih lijekova, pojavila se potreba za redefiniranjem tog pojma, djelomično zbog spoznaje da različite vrste moderne kompleksne onkoterapije mogu dovesti do velikoga broja KV komplikacija koje nisu ograničene samo na disfunkciju miokarda i zatajivanje srca (ZS). U nekim slučajevima onkološko liječenje može uzrokovati koronarnu bolest srca, hipertenziju, aritmije, bolesti zalistaka, tromboemboliju, abnormalnosti perikarda, a da ne spominjemo učinke novijih onkoloških postupaka kao što su imunoonkološki agensi koji mogu dovesti do miokarditisa, vaskulitisa ili stresne kardiomiopatije. Europsko kardiološko društvo je 2022. objavilo prve kliničke smjernice o kardioonkologiji utemeljene na dokazima koje, među ostalim, detaljno opisuju kardiotoksične nuspojave uzrokovane onkoterapijom i uvode novu definiciju toksičnosti onkološke terapije koja je proširena na cijeli KV sustav[8]. U ovome preglednom radu nastojimo pružiti obuhvatniji uvid u prethodne koncepte kardiotoksičnosti i nedavna objašnjenja tog pojma. Bolje znanje o kardiotoksičnosti može pridonijeti pravilnom praćenju KV bolesnika koji primaju onkološku terapiju kao i ranom otkrivanju i optimalnom upravljanju potencijalnim nuspojavama.

Kardiotoksičnost izazvana onkološkom terapijom – prethodne definicije

Tijekom posljednjih desetljeća objavljen je niz preporuka i dokumenata kako bi se izradile smjernice za kardiološki nadzor nad onkološkim bolesnicima. Dugo nisu postojali jasni i jedinstveni kriteriji za definiranje kardiotoksičnosti. U prvim se dokumentima promjena ejekcijske frakcije (EF) smatrala glavnom odrednicom CTRCD-a, ali nije bilo konsenzusa, ni dovoljno dobro definirane granične vrijednosti koja bi pomogla pri donošenju kliničkih odluka. Granica između normalne i abnormalne EF definirana je u nekim preporukama na 55 %[9], u drugima na 53 %[4,7] ili čak 50 %[5]. Stupanj promjene EF-a također se razlikovao u različitim radovima, a obično se smatralo da smanjenje od 10 % zavrjeđuje pozornost. U istraživanju nedavno objavljenu u Velikoj Britaniji uvedena je klasifikacija toksičnosti sa 6 kategorija, poznatija kao *Royal Brompton Hospital* klasifikacija[10]. U tom se sustavu kardiotoksičnost određuje ne samo promjenom na ejekcijskoj frakciji nego i promatranjem dijastoličke disfunkcije, globalne uzdužne deformacije (GLS), simptoma i mogućih promje-

anticancer treatments is one of the central issues in the field of cardio-oncology. These side effects may limit the success of oncotherapy and may also impair both the life expectancy and the quality of life of cancer patients. Several recommendations, statements and consensus documents have surfaced on this issue, providing various definitions of cardiotoxicity[2-6]. A precise and accurate definition of cardiotoxicity is not only important for nomenclature, but also a major decision factor in the further treatment of oncological patients. It is therefore important to define cardiotoxicity, as its diagnosis may lead to the temporary suspension or even permanent discontinuation of ongoing oncotherapy. Early definitions of cardiotoxicity focused on classical cancer therapy-related cardiac dysfunction (CTRCD) as the main component of adverse events, distinguishing between two distinct examples: type I cardiotoxicity caused by anthracyclines, previously considered irreversible, but nowadays considered reversible, and type II cardiotoxicity caused by trastuzumab, which is thought to be reversible by default[7]. Recent advances in scientific knowledge and the emergence of newer oncotherapeutic drugs necessitated the redefinition of this term, partly due to the recognition that various types of modern complex oncotherapy may lead to a wide range of cardiovascular complications, which are not limited to only myocardial dysfunction and heart failure. Various oncological treatments may, in some cases, cause coronary artery disease, hypertension, arrhythmias, valve disease, thromboembolism, pericardial abnormalities, not to mention the effects of newer oncological treatments such as immuno-oncological agents possibly leading to myocarditis, vasculitis or stress cardiomyopathy. In 2022, the European Society of Cardiology published the first evidence-based clinical practice guideline on cardio-oncology, which discusses in detail, among others, cardiotoxic side effects caused by oncotherapy, introducing a new definition of toxicity of anticancer therapy extended to the entire cardiovascular system[8]. In this summary, we aim to provide a broader view of the various earlier concepts of cardiotoxicity, as well as its recent interpretation. This knowledge may help to ensure both the proper cardiovascular monitoring of patients receiving oncotherapy and the early detection and optimal management of potential adverse events.

Oncotherapy-induced cardiotoxicity – prior definitions

Over the last decades, a number of recommendations and consensus documents have been published in an attempt to provide guidance for the cardiological surveillance of oncology patients. For a long time, there were no sufficiently sensitive, uniform set of criteria for defining cardiotoxicity. In the early documents, the change in ejection fraction (EF) was considered the main determinant of CTRCD, but there was no consensus or well-defined cut-off value to support clinical decision-making. The cut-off between normal and abnormal EF was defined in some recommendations at 55%[9], in other documents at 53%[4,7] or even 50%[5]. The degree of change in EF also differed in different papers, typically a 10% decrease was considered noteworthy. In a recent UK study, a 6-category toxicity classification, known as the Royal Brompton Hospital classification, was introduced[10]. In this system, the determination of cardiotoxicity was fine-tuned by taking into consideration diastolic dysfunction, global longitudinal strain (GLS),

na na biomarkerima. Takav je pristup u skladu s prethodno usvojenim europskim dokumentom o stajalištu koji, među ostalim, također poziva na Simpsonovu i 3D definiciju EF-a kako bi se izbjegle velike varijabilnosti među promatračima te uloga GLS-a i biomarkera u dijagnosticiranju ranog, čak i supkliničkog oštećenja[5]. Unazad nekoliko godina postalo je jasno da je još uvijek unatoč naporima teško prikupiti čvrste, na dokazima utemeljene i prognostički valjane podatke o KV parametrima u onkoloških bolesnika. Dobro definirane granične vrijednosti i precizna definicija kardiotoksičnih nuspojava od velike su važnosti jer, osim farmakoloških aspekata, mogu odrediti privremen ili čak trajan prekid antitumorskog liječenja, a time i klinički ishod osnovne bolesti. Poteškoće s prikupljanjem randomiziranih podataka bile su uglavnom uzrokovane vrlo visokom heterogenošću bolesnika i tijekom bolesti te nedostatkom standardiziranih istraživanja koja uključuju velike skupine bolesnika zbog različitih liječenja. S godinama su ipak objavljeni rezultati iz više manjih i srednjih retrospektivnih studija kao i iz registara.

Redefiniranje kardiotoksičnosti

Registar CARDIOTOX

Godine 2020. objavljeni su rezultati jednog od najvećih registara kardioonkoloških bolesnika pod nazivom *CARDIOTOX*[11] koji uključuje sedam centara, uglavnom u Španjolskoj. Istraživanje registra iskoristilo je dvogodišnje praćenje, a obuhvatilo je 865 bolesnika podvrgnutih onkološkoj terapiji s umjerenim do visokim rizikom od kardiotoksičnosti. Jedna od glavnih prednosti registra jest velika kohorta bolesnika koji su bili podvrgnuti različitim vrstama liječenja te činjenica da pojedinci s blagom do umjerenom KV bolešću nisu bili isključeni iz baze podataka, osim ako su imali očito ZS ili podatak o EF manjom od 40 %. Isto tako, nisu bili isključeni bolesnici s ranijim karcinomima i ranijom onkološkom terapijom. Posljedično tomu, rezultati iz registra bili su mnogo bliži stvarnim podatcima nego ikada prije. Primarni cilj registra bio je procijeniti rizik od kardiotoksičnosti, omogućiti ranu dijagnozu nuspojava i utvrditi prevalenciju kliničkih, biokemijskih i ehokardiografskih pokazatelja kardiotoksičnosti, kao i njihov odnos prema kriterijima ZS i preporukama za liječenje. Ukupno 865 od 1324 bolesnika bilo je uključeno u konačnu populaciju. Bolesnici s nepotpunim podatcima, ZS-om ili znatnim smanjenjem EF-a bili su isključeni iz istraživanja. Registar je podijeljen u 4 klase na temelju ozljede miokarda, disfunkcije, simptoma, abnormalnosti biomarkera i ehokardiografskih parametara: 1) normalna skupina nije imala abnormalnosti ni u jednom od promatranih parametara tijekom dvogodišnjega praćenja, 2) blaga skupina uključivala je bolesnike bez simptoma, s EF-om većim od 50 %, ali s povišenim razinama biomarkera ili drugim ehokardiografskim abnormalnostima, 3) umjerena kategorija uključivala je asimptomatske bolesnike s EF-om između 40 % i 50 %, s povišenjem biomarkera ili drugom disfunkcijom lijeve klijetke, 4) teška kategorija uključivala je asimptomatske bolesnike s EF-om manjim od 40 % ili bolesnike s kliničkim znakovima ZS-a, sa smanjenom, umjereno smanjenom ili očuvanom vrijednosti EF-a. Kardiotoksičnost je definirana kao pojava novog ili pogoršanje postojećeg oštećenja miokarda ili disfunkcija zbog koje je bolesnika potrebno premjestiti iz jedne klase u višu tijekom praćenja. Nakon detaljnih analiza otkrivena je kardiotoksičnost u oko 37,5 % bolesnika, i to blaga u 31,6 %, umjerena u 2,8 % i teška u 3,1 % slučajeva. Nešto viša životna dob uočena je u skupini

symptoms, and possible changes in cardiac biomarkers, in addition to the EF. This was in line with the previous European position paper, which, among other points, also called for Simpson and 3-dimensional EF definition to avoid high intra- and interobserver variability, and the role of GLS and biomarkers to diagnose early, even subclinical impairment[5]. By the 2020s, it has become clear that, despite several efforts, it is still difficult to obtain solid, evidence-based, prognostically valid data on cardiovascular parameters in oncology patients. However, well-defined cut-off values and the precise definition of cardiotoxic side effects are of great importance, since, apart from pharmacological aspects, they may determine the temporary or even permanent interruption of the patient's anticancer treatment and thus, the clinical outcome of the underlying disease. The difficulty in collecting randomised data was mainly due to the very high heterogeneity of patients and disease courses, and also to the lack of standardised studies including large patient cohorts due to the diversity of treatments. However, over the years, more and more results have been presented from small-item prospective and medium-item retrospective observational analyses and registry data.

Redefining cardiotoxicity

CARDIOTOX registry

In 2020, one of the largest registries of cardio-oncology patient cohorts to date, called CARDIOTOX, was published[11], involving a total of 7 centres, mainly in Spain. The registry study, which used a two-year follow-up, included 865 patients undergoing oncotherapy with a moderate to high risk of cardiotoxicity. One of the major advantages of the registry was that it examined a large cohort of patients undergoing various treatments, and that individuals with mild to moderate cardiovascular disease were not excluded from the database unless they had manifest heart failure or a history of EF below 40%. Similarly, no previous cancer or cancer therapy was excluded. Consequently, the results from the registry were much closer to real-life data than before. The primary objective of the registry was to assess the risk of cardiotoxicity, to provide an early diagnosis of adverse events, and to determine the prevalence of clinical, biochemical and echocardiographic indicators of cardiotoxicity and their relationship to current heart failure criteria and treatment recommendations. A total of 865 of 1324 patients were included to form the final patient population. Those with incomplete data, heart failure or substantial EF reduction were excluded from the study. The registry was divided into 4 classes based on myocardial injury, dysfunction, symptoms, cardiac biomarker abnormalities and cardiac ultrasound parameters: 1) the normal group had no abnormalities in any of the studied parameters during the two-year follow-up, 2) the mild group included patients with no symptoms, an EF above 50% but elevated biomarker levels or other cardiac ultrasound abnormalities, 3.) the moderate category included asymptomatic patients with an EF between 40-50%, with biomarker elevation or other left ventricular dysfunction, 4) the severe category included asymptomatic patients with an EF below 40% or those with clinical signs of heart failure, with reduced, moderately reduced or preserved EF. Cardiotoxicity was defined as the onset of new or worsening myocardial damage or dysfunction when a patient was transferred from one class to a higher class during follow-up. After detailed analyses, cardiotoxicity was detected in about

s teškim nuspojavama. Što se tiče spola, većina bolesnika bile su žene s rakom dojke, od kojih je oko 85 % primalo antraciklin, a 21 % HER2 inhibitor. Što se tiče kardioprotektivne terapije, 39 % bolesnika je već uzimalo jedan od osnovnih lijekova prije istraživanja, dok se tijekom praćenja taj broj povećao na 70 %. Utvrđeno je da je rizik od kardiotoksičnosti bio povećan ako je bolesnik imao anamnestički podatak o prethodnom karcinomu ili onkološkom liječenju, ili nižu početnu vrijednost EF-a i GLS-a. Na temelju rezultata registra, pogoršanje EF-a od 10 % ili smanjenje EF-a na manje od 40 % bilo je relativno rijetko u cijeloj kohorti, dok su povećanja vrijednosti troponina i smanjenja GLS-a bili mnogo učestaliji. Preživljenje bolesnika bez kardiotoksičnih nuspojava i onih s blagim do umjerenim nuspojavama bilo je mnogo bolje u usporedbi s onima s teškim nuspojavama (**slika 1**). Ukratko, prema novoj definiciji kardiotoksičnosti utvrđenoj u istraživanju registra *CARDIOTOX*, prolazna ili trajna disfunkcija miokarda pojavila se u relativno visokom postotku bolesnika. Međutim, teška kardiotoksičnost od velike prognostičke važnosti povezana s povećanom smrtnošću bila je relativno rijetka. Nužno je da se ovi rezultati odraze u kliničkoj praksi, jer upućuju na to da će se najvjerojatnije razmatrati prekid onkološke terapije ako su prisutne ili se žele prevenirati teške KV komplikacije čija je incidencija, nasreću, niska. Klasifikacija u 4 klase jednostavna je i laka za primjenu, a prednosti u pogledu smrtnosti uglavnom se očekuju ako se bolesnici u kojih se očekuju ozbiljne kardiotoksične nuspojave mogu ranije otkriti. Ako želimo dijagnosticirati kardiotoksičnost s čak i prolaznom ozljedom miokarda ili disfunkcijom u supkliničkoj fazi, nije dovoljno pratiti samo EF izmjeren konvencionalnom dvodimenzionalnom ehokardiografijom tijekom onkološkog liječenja. Za rano otkrivanje blagih do umjerenih abnormalnosti uz rutinske pretrage ne smiju izostati kardiološki biomarkeri i sofisticirani ehokardiografski parametri (3-dimenzionalni EF, GLS, tkivni dopler).

37.5% of patients, with mild in 31.6% of cases and moderate or severe in 2.8% and 3.1% of cases, respectively. A slightly higher age was observed in the group with severe side effects. In terms of gender, most patients were women with breast cancer, of whom about 85% received anthracycline and 21% HER2 inhibitor treatment. Regarding cardioprotective therapy, 39% of patients were already taking one of the baseline drugs before the study, while this number increased to about 70% during follow-up. It was found that the risk of cardiotoxicity was increased if the patient had a history of previous cancer or oncological treatment, or a lower baseline EF and GLS. Based on the registry results, a 10% worsening of EF or a decrease in EF below 40% was relatively rare in the entire cohort, whereas increases in cardiac troponin and decreases in GLS were much more common. Survival of patients free from cardiotoxic side effects and those with mild to moderate side effects was significantly better compared to those with severe side effects (**Figure 1**). In summary, under the new definition of cardiotoxicity established in the CARDIOTOX registry study, transient or permanent myocardial dysfunction occurred in a relatively high percentage of patients; however, severe cardiotoxicity of strong prognostic relevance associating with increased mortality was relatively rare. It is necessary to reflect these findings in clinical practice, as they suggest that discontinuation of oncotherapy is most likely to be considered in the presence or prevention of mainly severe cardiovascular complications, the incidence of which is fortunately low. The classification into 4 classes is simple and easy to use, with mortality benefits mainly expected if patients susceptible to serious cardiotoxic side effects can be screened early. If we wish to diagnose cardiotoxicity with even transient myocardial injury or dysfunction at a subclinical stage, it is not sufficient to follow just the EF measured by conventional 2-dimensional echocardiography during the oncological treatment. In addition

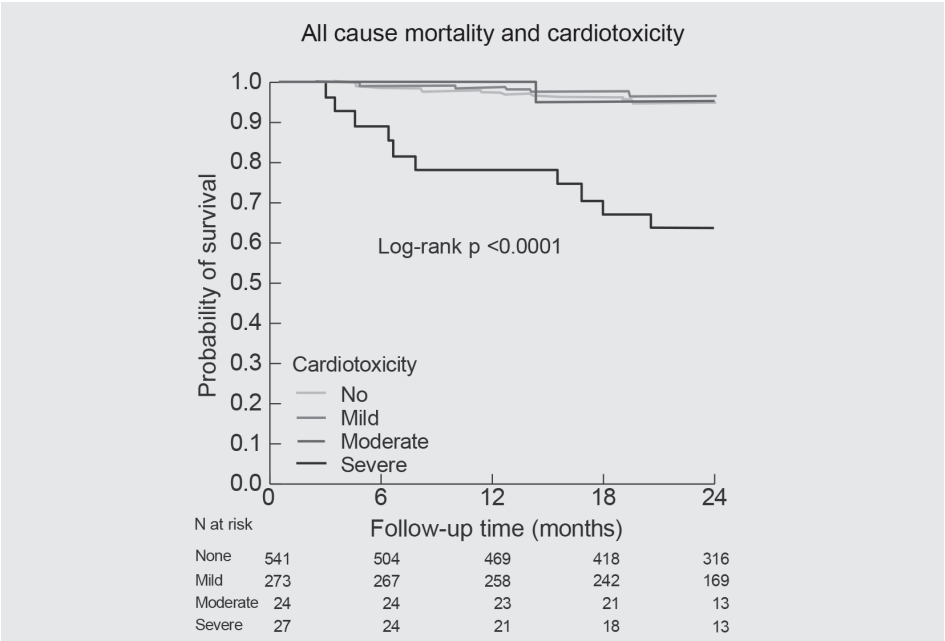

FIGURE 1. Among patients enrolled in the CARDIOTOX registry, survival is significantly better in patients not diagnosed with a cardiotoxic side effect or in those with mild to moderate adverse effects compared to patients with severe side effects. Adapted from López-Sendón *et al.*[11]

Kardiovaskularna toksičnost redefinirana u kliničkim smjernicama Europskoga kardiološkog društva

Nedavno su prve kliničke kardio-onkološke smjernice, već potkrijepljene razinama dokaza i klasama preporuka, objavljene pod pokroviteljstvom Europskoga kardiološkog društva u suradnji s nekoliko velikih međunarodnih organizacija[8]. Autori ovog dokumenta pokušali su odgovoriti na brojna pitanja koja se pojavljuju u svakodnevnoj praksi tijekom kardiološkoga zbrinjavanja bolesnika na onkološkoj terapiji i onih koji su preživjeli karcinom. Među ostalim, uključeni su algoritmi za klasifikaciju rizika u onkoloških bolesnika, dodatni klinički zadatci prema stratifikaciji rizika, proširene nove definicije KV toksičnosti te preporuke za prevenciju, liječenje i praćenje. Dokument i dalje preporučuje uporabu prethodno korištenog izraza CTRCD za označivanje oštećenja miokarda, disfunkcije miokarda i ZS-a povezanih s onkološkim liječenjem. Istodobno, nedavno uveden međunarodni termin CTR-CVT (KV toksičnost povezana s onkološkom terapijom) predložen je za definiranje štetnih događaja koji utječu na bilo koji dio KV sustava[12]. CTR-CVT uključuje 5 najčešćih KV komplikacija uzrokovanih antitumorskom terapijom: 1) disfunkcija miokarda i ZS, 2) miokarditis, 3) vaskularna toksičnost, 4) hipertenzija, 5) aritmije i produljenje korigiranog QT intervala (QTc). Dokument posebno navodi definiciju toksičnosti za svaku skupinu, često naglašujući težinu abnormalnosti te je li riječ o simptomatskom ili asimptomatskom štetnom događaju. U slučaju asimptomatske disfunkcije miokarda, razlikujemo blagi, umjereni i teški stadij, dok su za simptomatsko ZS kategorije blaga, umjerena, teška i vrlo teška. Oni se razlikuju s obzirom na simptome, EF, GLS, biomarkere, potrebu za intenziviranje liječenja, nužnost bolničkog liječenja i, u najtežim slučajevima, potrebu za inotropnom i/ili mehaničkom potporom cirkulacije ili transplantacijom srca (**tablica 1**). Miokarditis je najvažnija nuspojava liječenja inhibitorima imunosnih kontrolnih točaka (ICI). U kliničkoj dijagnozi miokarditisa prisutnost dijagnostičkih obilježja upale miokarda otkrivenih MR-om srca kao glavnim kriterijem, ili povezanost povišenja troponina s dva manja kriterija imaju važnu ulogu: klinički znakovi, ventrikularne aritmije i/ili poremećaji provođenje, sistolička disfunkcija lijeve klijetke s poremećajima kontraktilnosti ili bez njih (ne po tipu Takotsubo), druge imunosno posredovane komplikacije (miozitis, miopatija, mijastenija), sumnja na upalu miokarda otkrivena MR-om srca. Što se tiče ozbiljnosti, miokarditis izazvan ICI-jem dijeli se na fulminantni, nefulminantni i refraktorni na liječenje velikim dozama steroida. Unutar skupine vaskularne toksičnosti nalaze se: asimptomatska ateroskleroza (koronarna, periferna, karotidna), tromboza (venska, arterijska) i poremećaj vazoreaktivnosti (periferna, koronarna makrovaskularna ili mikrovaskulatura); koje se razlikuju od simptomatske toksičnosti kao što su TIA / moždani udar, akutni ili kronični koronarni sindrom, periferna arterijska bolest, vazospastična ili mikrovaskularna angina i Raynaudova bolest. Što se tiče hipertenzije, potreba za privremenim prekidom liječenja tumora definirana je ako je arterijski tlak (AT) viši od 180/110 mmHg, a inače se preporučuje kontrola AT lijekovima pri vrijednostima većima od 140/90 mmHg i 130/80 mmHg u bolesnika s visokim KV rizikom. Za aritmije se upućuje na postojeće europske smjernice. U QTc rasponu od 480 do 500 ms preporučuju se veći oprez, korekcija reverzibilnih uzroka, nadoknada elektrolita i prekid uzimanja drugih sredstava koji produljuju PQ interval, dok se

to routine examinations, the use of cardiac biomarkers and sophisticated echocardiographic parameters (3-dimensional EF, GLS, tissue Doppler) seems indispensable for the early detection of mild to moderate abnormalities.

Cardiovascular toxicity redefined in the clinical guidelines of the European Society of Cardiology

Recently, the first clinical guideline on cardio-oncology, already supported by levels of evidence and classes of recommendation, has been published under the auspices of the European Society of Cardiology in collaboration with several major international societies[8]. The authors of this document have attempted to provide answers to a wide range of questions arising in daily practice during the cardiological management of patients receiving oncological treatment and cancer survivors. Among other things, algorithms for the risk classification of patients undergoing oncological treatment, additional clinical tasks according to risk stratification, expanded new definitions of cardiovascular toxicity, as well as recommendations for prevention, treatment and follow-up are included. The document continues to recommend the use of the previously used term CTRCD to refer to myocardial damage, myocardial dysfunction and heart failure associated with the oncological treatment. At the same time, the recently introduced international term CTR-CVT (cancer therapy-related cardiovascular toxicity) is proposed to define adverse events affecting any part of the cardiovascular system[12]. CTR-CVT includes the 5 most common cardiovascular complications caused by anticancer therapy: 1) myocardial dysfunction and heart failure, 2) myocarditis, 3) vascular toxicity, 4) hypertension, 5) arrhythmias and corrected QT interval (QTc) prolongation. The definition of toxicity for each group is specifically detailed in the document, often with a strong emphasis on the severity of the abnormality and whether it is a symptomatic or asymptomatic adverse effect. In the case of myocardial dysfunction, a distinction is made between mild, moderate and severe but asymptomatic, while for symptomatic heart failure, the categories are mild, moderate, severe and very severe. These are differentiated on the basis of symptoms, EF, GLS, cardiac biomarkers, the need to consider intensification of therapy, the necessity of hospital setting, and in the most severe cases, the need for inotropic and/or mechanical circulatory support or cardiac transplantation (**Table 1**). In the case of myocarditis, the side effects of immune checkpoint inhibitor (ICI) treatments are of utmost importance. In the clinical diagnosis of myocarditis the presence of diagnostic characteristics of myocardial inflammation detected by cardiac MR imaging as major criteria, or the association of troponin elevation with two minor criteria plays an important role: clinical signs, ventricular arrhythmias and/or conduction disturbances, left ventricular systolic dysfunction with or without regional wall motion abnormality (non-Takotsubo type appearance), other immune-mediated complications (myositis, myopathy, myasthenia), suspected myocardial inflammation detected by cardiac MR. In terms of severity, ICI-induced myocarditis is differentiated into fulminant, non-fulminant and refractory to high-dose steroid treatment. Within the vascular toxicity group, asymptomatic atherosclerosis (coronary, peripheral, carotid), thrombosis (venous, arterial) and vasoreactivity disorder (peripheral, coronary macro- or microvasculature) are distinguished from symptomatic toxicity such as TIA/stroke, acute or chronic coronary syndrome, peripheral

TABLE 1. Cancer therapy-related cardiac dysfunction in the 2022 European Society of Cardiology guidelines on cardio-oncology.

Symptomatic CTRCD	Very severe	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
	Severe	HF hospitalization
	Moderate	Need for outpatient intensification of diuretic and HF therapy
	Mild	Mild HF symptoms, no intensification of therapy required
Asymptomatic CTRCD	Severe	New LVEF reduction to <40%
	Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40-49% OR New LVEF reduction by <10 percentage points to an LVEF of 40-49% AND either new relative decline in GLS by >15% from baseline OR new rise in cardiac biomarkers
	Mild	LVEF ≥50% AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers

CTRCD = cancer therapy-related cardiac dysfunction; HF = heart failure; LVEF = left ventricular ejection fraction; GLS = global longitudinal strain[8]

za QTc dulji od 500 ms preporučuju prekid terapije i razmatranje smanjenja doze ili alternativnog liječenja.

Buduće perspektive – precizna medicina

Iz opisanih je nalaza jasno da su KV nuspojave povezane s onkološkom terapijom velik izazov i liječnicima i bolesnicima. Učestalost i dugoročne učinke KV toksičnosti teško je predvidjeti, a oni mogu biti od prolaznih do trajnih. Ono što dodatno komplicira proučavanje nuspojava jest znatna varijabilnost među bolesnicima i činjenica da nuspojave uzrokovane različitim načinima liječenja izazivaju različite simptome koji nastaju preko različitih patomehanizama. Precizna medicina dobiva sve veću pozornost u prevladavanju ovakvih izazova personalizacijom onkološke terapije, a time i u prevenciji ili ublažavanju KV toksičnosti. Precizna je medicina oblik medicine koji se koristi informacijama o vlastitim genima ili proteinima pojedinca za prevenciju, dijagnosticiranje ili liječenje bolesti. Ona predlaže prilagođivanje zdravstvene skrbi tako što se preporučuju medicinske odluke, liječenja, strategije prevencije, skrb ili lijekovi/proizvodi jednoj ili više pojedinačnih podskupina, čime se izbjegava uniformiran pristup svim bolesnicima[13]. Pojavom platformi precizne medicine u onkologiji i kardiologiji, precizna kardioonkologija također izrasta u prijeko potreban koncept koji uzima u obzir sljedeća tri čimbenika u liječenju bolesnika: KV rizik bolesnika, sam tumor i plan onkološkog liječenja. Ta se tri čimbenika mogu iskoristiti za predviđanje s dobrim izgledima pojave i oblika KV toksičnosti, što može poboljšati kvalitetu kardioonkološke skrbi[14]. Procjena rizika od KV toksičnosti može biti dodatno potpomognuta podatcima iz precizne medicine, kao što su genetika, farmakogenomika, proteomika i radiomika, koji se mogu ugraditi u karakterizaciju KV biologije pojedinca. Precizna kardioonkologija također privlači sve veću pozornost istraživača. Značajan istraživački napor uključuje uporabu inducibilnih pluripotentnih matičnih stanica koje se mogu diferencirati u kardiomiocite pri mapiranju rizika od KV toksičnosti od onkološkog agensa bez potrebe za stvarnom onkološkom terapijom. To omogućuje precizniji odabir sigurnijih onkoloških postupaka s nižim indeksom kardiotoksičnosti

arterial vascular disease, vasospastic or microvascular angina, and the Raynaud's phenomenon. Regarding hypertension, the need for temporarily suspending anticancer treatment is defined as blood pressure (BP) beyond 180/110 mmHg, otherwise, the control of BP with medication is recommended at values above 140/90 mmHg and 130/80 mmHg in patients at high cardiovascular risk. For arrhythmias, reference is made to the current European guidelines. In the QTc range of 480-500 ms, increased alert, correction of reversible causes, electrolyte replacement and discontinuation of other QT-prolonging agents are recommended, while for a QTc longer than 500 ms, discontinuation of therapy and consideration of dose reduction or alternative treatment is necessary.

Future perspectives – precision medicine

From the above findings, it is clear that cardiovascular side effects from oncotherapy pose a great challenge to both clinicians and patients. The incidence and long-term effects of cardiovascular toxicity are difficult to predict and may be transient or irreversible. What further complicates the studying of adverse effects is the considerable variability between patients and the fact that adverse effects caused by different treatments induce various symptoms, which arise via different pathomechanisms. Precision medicine is gaining increasing attention in overcoming these challenges by personalising oncotherapy and thus, in preventing or alleviating cardiovascular toxicity. Precision medicine is a form of medicine that uses information about an individual's own genes or proteins to prevent, diagnose or treat disease. Precision medicine proposes the tailoring of healthcare by recommending medical decisions, treatments, prevention strategies, care or drugs/products of choice to one or more individual subgroups of patients, avoiding a "one-size-fits-all" model[13]. With the emergence of precision medicine platforms in oncology and cardiology, precision cardio-oncology has also become a necessary concept that takes into consideration the following three factors when treating patients: the patient's cardiovascular risk, the tumour itself, and the oncology treatment plan. These can be used to predict with a good chance the occurren-

za određenog bolesnika, čime se rizik od kardiotoksičnosti smanjuje na najmanju razinu. Osim toga, matične stanice iz većih populacija mogu se čak uporabiti za razvoj novih lijekova i terapijskih opcija s niskim indeksom kardiotoksičnosti kao prioritetom[15].

Zaključci

Kardioonkologija je dinamična specijalizacija koja se razvija i čiji je glavni cilj promicanje uspješne onkološke terapije, dugoročnoga preživljavanja i bolje kvalitete života onkoloških bolesnika. Tijekom proteklih desetljeća stečeno je opsežno znanje na ovom području koje je pomoglo da se preciznije definiraju KV nuspojave antitumorskih terapija, uzimajući u obzir njihovu ulogu u kliničkoj prognozi. Precizna će definicija uvelike pridonijeti boljim terapijskim intervencijama u praćenju bolesnika s poboljšanjem kliničke prognoze. Nova definicija KV toksičnosti uzima u obzir ozbiljnost kliničkih abnormalnosti i prisutnosti, odnosno odsutnosti simptoma. Primjena nove definicije u otkrivanju nuspojava i procjeni rizika od kardiotoksičnosti može uvelike unaprijediti kvalitetu kardioonkološke skrbi i dugoročnu prognozu bolesnika.

ce and form of cardiovascular toxicity, which may improve the quality of cardio-oncology care[14]. Estimating cardiovascular toxicity risk can be further aided by data from precision medicine, such as genetics, pharmacogenomics, proteomics and radiomics, which can be incorporated to characterise the cardiovascular biology of an individual. Precision cardio-oncology is also drawing increasing attention among basic researchers. A significant part of these research efforts involve the use of inducible pluripotent stem cells, which can be differentiated into cardiomyocytes to map the risk of cardiovascular toxicity from an oncological agent without the need for actual oncological therapy yet. This allows a more precise selection of safer oncological treatments with a lower cardiotoxicity index for a given patient, thus minimising the risk of cardiotoxicity. In addition, stem cells from larger populations may even be used to develop novel drugs and therapeutic options with a low cardiotoxicity index as a priority[15].

Conclusions

Cardio-oncology is a dynamic and evolving discipline with the main goal of promoting successful oncotherapy, long-term survival and improved quality of life for cancer patients. Over the past decades, a large body of knowledge has been accumulated in this field, which has helped to define the cardiovascular side effects of anticancer therapies more precisely, taking into account their role in clinical prognosis. A precise definition will greatly support appropriate therapeutic interventions and patient follow-up for better clinical prognosis. The recently redefined definition of cardiovascular toxicity takes into account both the severity of clinical abnormalities and the presence or absence of symptoms. The use of this new definition to detect adverse events and to assess a patient's risk of cardiotoxicity may greatly improve the quality of cardio-oncology care and the long-term prognosis of patients.

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