Kardiotoksičnost kao posljedica biološke terapije tumora

Cardiotoxicity due to biological cancer therapy

Ivo Darko Gabrić*

Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska

University Hospital Centre "Sestre milosrdnice", Zagreb, Croatia

SAŽETAK: Kardiotoksičnost je sve češća nuspojava onkološkog liječenja pa tako i novijih, bioloških ciljanih lijekova. Posebno razvijena monoklonska protutijela ili inhibitori tirozin-kinaze blokiraju bilo receptore HER-2 bilo VEGF bilo pak aktivnost Abl-kinaze. Međutim, time se ometaju i molekularni mehanzimi ključni za kardiovaskularno zdravlje. Anti-HER2 terapija najčešće uzrokuju reverzibilnu sistoličku disfunkciju lijevog ventrikula, a blokadom VEGF receptora razvija se arterijska hipertenzija i povećava sklonost tromboembolijskim incidentima. Ranim prepoznavanjem i liječenjem bolesnika u kojih se razvila kardiotoksičnost postiže se poboljšanje kliničkih ishoda i kvalitete života, a time je često moguće nastaviti specifično liječenja raka. Pri tome su ključni multidisciplinarni pristup kardiologa i onkologa te redovito kardiološko praćenje.

SUMMARY: Cardiotoxicity has been increasingly reported as a side effect of oncologic treatment, including novel targeted biological therapy. Specific monoclonal antibodies or tyrosine kinase inhibitors have been developed for blockade of HER2 receptors, VEGF receptors, or Abl kinase activity. However, these actions also interfere with molecular mechanisms that are crucial for cardiovascular health. Anti HER2 therapy generally induces reversible systolic left ventricular dysfunction, whereas VEGF receptor blockade leads to development of arterial hypertension and increased susceptibility to thromboembolic events. In patients developing cardiotoxicity, better clinical outcome and quality of life can be achieved by early recognition and treatment, thus also enabling continuation of anti-cancer therapy in many cases. A multidisciplinary approach including cardiologists and oncologists, along with regular cardiologic follow up, is crucial for successful patient management.

KLJUČNE RIJEČI: kardiotoksičnost, kardioonkologija, biološka terapija tumora, inhibitori tirozin-kinaze.

KEYWORDS: cardiotoxicity, cardio-oncology, tumor biological therapy, tyrosine kinase inhibitors.

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***ADDRESS FOR CORRESPONDENCE:** Ivo Darko Gabrić, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, HR-10000 Zagreb, Croatia. / Phone: +385-1-3787-111 / E-mail: idgabric@gmail.com

ORCID: Ivo Darko Gabrić, http://orcid.org/0000-0003-4719-4634

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Mortalitet od malignih bolesti smanjen je u proteklih 30 godina, među ostalim i zbog napretka kemoterapijskih protokola.[1] Poboljšanje preživljenja međutim često je na štetu oštećenja drugih organa, uključujući i kardiovaskularni (KV) sustav[2] te su danas KV bolesti drugi vodeći uzrok dugoročnog pobola i smrtnosti među bolesnicima liječenima zbog karcinoma.[3] Konvencionalnom kemoterapijom, kao i ciljanom biološkom terapijom povećava se rizik od srčanog oštećenja, disfunkcije lijeve klijetke (LV) i simptomatskog zatajivanja srca (ZS).[4] Također se mogu razviti hipertenzivna reakcije, vazospastična i/ili trombotska ishemija miokarda te poremećaj ritma i provođenja. Neki su od tih štetnih učinaka ireverzibilni i uzrokuju progresivnu KV bolest, a neki izazivaju samo privre-

In the past 30 years, malignant disease mortality has been reduced, among other things, owing to advances in chemotherapeutic protocols.[1] However, prolonged survival frequently is achieved at the expense of damage to other organs including cardiovascular (CV) system.[2] Currently, CV diseases are the second leading cause of long-term morbidity and mortality among patients treated for carcinoma.[3] Both conventional chemotherapy and targeted biological therapy increase the risk of heart injury, left ventricular (LV) dysfunction and symptomatic heart failure (HF).[4] In addition, hypertensive reaction, vasospastic and/or thrombotic myocardial ischemia, rhythm and conductivity disorders may also occur. Some of these adverse effects are irreversible and cause progressive CV disease, whereas others cause

menu disfunkciju bez dugoročnih posljedica.[5] Predispozicija za razvoj kardiotoksičnosti je multifaktorska i određena interakcijom genskih i okolišnih čimbenika.[6] Kardiotoksičnost se može očitovati tijekom ili neposredno nakon liječenja (u nekoliko dana ili tjedana), ali i dulje vrijeme nakon završetka antitumorske terapije. Neki od definiranih čimbenika rizika jesu pozitivna obiteljska anamneza koronarne bolesti srca ili kongestivnog ZS-a, dob, spol, arterijska hipertenzija i dislipidemija. Također je utvrđeno da je povećan rizik od razvoja kardiotoksičnosti u bolesnika sa smanjenom sistoličkom funkcijom LV-a te značajnim aritmijama.

Kako se sve veći broj bolesnika liječi kemoterapijom i biološkim lijekovima, incidencija kardiotoksičnosti kontinuirano raste.[7] Opseg problema još je veći jer dio bolesnika mora uzimati kombinaciju više kardiotoksičnih lijekova.[8] Stoga se vidjelo da postoji potreba formiranja kardio-onkoloških timova, kao i definiranja smjernica za praćenje i liječenje takvih bolesnika, poput onih iz 2016. godine koje je nedavno objavilo Europsko kardiološko društvo.[9]

Biološka terapija tumora monoklonskim protutijelima ili inhibitorima tirozin-kinaze (TKI) (**tablica 1**) usmjerena je bilo

only transient dysfunction without long-term sequels.[5] Predisposition to development of cardiotoxicity is multifactorial and is determined by the interaction of genetic and environmental factors.[6] Cardiotoxicity may manifest during or immediately after treatment (within days or weeks), or even long after completion of anti-cancer therapy. Some of the defined risk factors are for coronary artery disease or congestive HF positive family history, age, sex, arterial hypertension and dyslipidemia. An increased risk of cardiotoxicity has also been reported in patients with reduced systolic LV function and significant arrhythmias.

The ever-growing number of patients treated with chemotherapy and biological agents has resulted in the continuously increasing incidence of cardiotoxicity.[7] The extent of the problem is even greater taking into account that some of the patients have to take a combination of several cardiotoxic agents.[8] These unfavorable facts have pointed to the need of establishing cardio-oncologic teams and defining guidelines for follow up and treatment of these patients, such as those recently issued by the European Society of Cardiology in 2016.[9]

Tumor biological therapy with monoclonal antibodies or tyrosine kinase inhibitors (TKI) targets human epidermal growth

TABLE 1. Factors associated with risk of cardiotoxicity and incidence of left ventricular dysfunction following anti-HER2 compounds and VEGF inhibitors. Modified from Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. Eur Heart J. 2016 Sep 21;37(36):2768-2801.

Agent	Incidence of left ventricular dysfunction (%)	Risk factors
Anti-HER2 compounds		
Antibodies		Previous or concomitant anthracycline treatment (short time between anthracycline and anti-HER2 treatment) Age (>65 years) High body mass index >30 kg/mg^2 Previous left ventricular dysfunction Arterial hypertension Previous radiation therapy
Trastuzumab	1.7-13	
Pertuzumab	0.7-1.2	
Trastuzumab emtansine (T-DM1)	1.7	
Tyrosine kinase inhibitors		
Lapatinib	0.2-1.5	
VEGF inhibitors		
Antibodies		Pre-existing heart failure, significant coronary artery disease or left side valvular heart disease (e.g. mitral regurgitation), chronic ischemic cardiomyopathy Previous anthracycline
Bevacizumab	1.6-4	
Ramucirumab		
Tyrosine kinase inhibitors		
Sunitimib	2.7-19	Arterial hypertension Pre-existing cardiac disease
Pazopanib	7-11	
Axitinib		
Neratinib		
Sorafenib	4-8	
Dasatinib	2-4	

HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor.

na receptore humanoga epidermalnog faktora rasta 2 (HER-2) (npr. trastuzumab, pertuzumab itd.), vaskularni endotelni faktor rasta (VEGF) i VEGF receptor (npr. bevacizumab, sunitinib, sorafenib itd.) te aktivnost Abl-kinaze (npr. imatinib, nilotinib, dasatinib, itd).[10] Međutim, time se ometaju i molekularni mehanizmi ključni za KV zdravlje te se razvija kardiotoksičnost. Svrha je ovoga članka navesti potencijalne KV nuspojave vezane za pojedine biološke lijekove i protutijela koji se rabe u liječenju raka u odraslih.

Trastuzumab

Trastuzumab je humanizirano monoklonsko protutitijelo na HER2 receptor stanične površine koje inhibira prijenos signala induciranog aktivacijom humanoga epidermalnog faktora rasta.[11,12] Utvrđeno je da blokiranje HER2 receptora u bolesnica s karcinomom dojke koje imaju prekomjernu ekspresiju HER2 receptora znatno poboljšava preživljenje, kao i vrijeme remisije te se primjenjuje u standardnom protokolu liječenja metastatske ili lokalne bolesti.[13,14] Najvažnija nuspojava terapije trastuzumabom jest pojava kardiotoksičnosti koja je neovisna o kumulativnoj dozi lijeka i najčešće se očituje u asimptomatskom smanjenju istisne frakcije lijeve klijetke (EFLV), a manje često u klinički simptomatskom ZS-u.[15] Za razliku od ireverzibilnog (tip I.) oštećenja uzrokovana antraciklinima, zbog liječenja trastuzumabom u većine oboljelih nastaje reverzibilna "ošamućenost" (eng. *stunning*) srca koja se u 65 – 70 % bolesnika oporavi unutar 30 dana (tip II.).[16] Ipak, moguća je i progresija do razvoja ireverzibilne dilatacijske kardiomiopatije. Incidencija kardiotoksičnosti kreće se, prema velikim studijama, od 8 do 13 %, a slične podatke pokazuju i metaanalize randomiziranih kontroliranih studija u kojima je učestalost kardiotoksičnosti oko 10 %.[17,18] Čini se da je kardiotoksičnost većim dijelom uzrokovana izravnom blokadom HER2 proteina u srcu, iako su mogući i drugi mehanizmi.[19] Čimbenici rizika za razvoj kardiotoksičnosti jesu ranija arterijska hipertenzija, niža EFLV na početku liječenja trastuzumabom, visoki indeks tjelesne mase (BMI > 25), koronarna i valvulna bolest te prethodno liječenje višim dozama antraciklina.[20,21]

Incidencija, kao i oblik kardiotoksičnosti drugih anti-HER2 bioloških lijekova (pertuzumab i trastuzumab-emtanzin), u pravilu su slični trastuzumabu.[22] U novijim protokolima neoadjuvantne terapije raka dojke, kao i pri liječenju metastatskog raka želudca, trastuzumab se kombinira s drugim anti-HER2 lijekovima. Te kombinacije, prema dosadašnjim podatcima, nisu uzrokovale dodatno pogoršanje KV nuspojava.[23] Ipak, očekuju se rezultati velike, prospektivne, randomizirane studije (*APHINITY*) koja ispituje kombinaciju pertuzumaba i trastuzumaba u adjuvantnom liječenju.[24] Dvije studije neoadjuvantne terapije (*NeoSphere*, *TRYPHAENA*) pokazale su bolje rezultate u žena s rakom dojke liječenih kemoterapijom i dvojnom HER2 blokadom (pertuzumab, trastuzumab) u usporedbi s onima liječenima samo kemoterapijom i trastuzumabom. U studiji *TRYPHANEA* postignut je primarni cilj KV sigurnosti s niskom incidencijom simptomatske i asimptomatske sistoličke disfunkcije LV-a u svim ispitivanim skupinama.[25] Treba na kraju napomenuti da je korist od trastuzumaba u smislu smanjenja rizika od osnovne zloćudne bolesti veća od povećanog rizika za razvoj kardiotoksičnosti.

factor 2 (HER2) receptors (e.g., trastuzumab, pertuzumab, etc.), vascular endothelial growth factor (VEGF) and VEGF receptors (e.g., bevacizumab, sunitinib, sorafenib, etc.), or Abl kinase activity (e.g., imatinib, nilotinib, dasatinib, etc.)[10] (**Table 1**). However, these therapies also impair molecular mechanisms that are crucial for CV health, resulting in cardiotoxicity. The aim of the article is to point to the potential CV side effects associated with particular biological drugs and antibodies used in the treatment of carcinoma in adult patients.

Trastuzumab

Trastuzumab is a humanized monoclonal antibody that targets human epidermal HER2 receptor by inhibiting transfer of the signal induced by HER2 activation.[11,12] In breast cancer patients with HER2 receptor overexpression, HER2 receptor blockade was found to improve survival and time of remission significantly, and has been used in the standard treatment protocol for metastatic or localized disease.[13,14] The major side effect of trastuzumab therapy is the occurrence of cardiotoxicity independent of the drug cumulative dose, mostly manifesting as asymptomatic reduction of the left ventricular ejection fraction (LVEF), and less frequently as clinically symptomatic HF.[15] Unlike irreversible (type I) anthracycline induced damage, trastuzumab therapy results in reversible cardiac stunning in most cases, which resolves within 30 days (type II) in 65%-70% of patients.[16] However, in some patients it may progress to irreversible dilated cardiomyopathy. In large studies, the incidence of cardiotoxicity ranges from 8% to 13%, and similar data have also been reported from meta-analyses of randomized controlled studies, where the incidence of cardiotoxicity was around 10%.[17,18] It appears that cardiotoxicity is mostly caused by direct cardiac HER2 protein blockade, however, other mechanisms cannot be excluded.[19] Risk factors for development of cardiotoxicity are pre-existent arterial hypertension, low LVEF at initiation of trastuzumab therapy, high body mass index (>25), coronary and valvular disease, and previous treatment with high anthracycline doses.[20,21]

The incidence and type of cardiotoxicity of other anti-HER2 biological agents (pertuzumab and trastuzumab-emtansine) generally are similar to those associated with trastuzumab.[22] In recent protocols of neoadjuvant therapy for breast cancer and in the treatment of metastatic gastric cancer, trastuzumab is combined with other anti-HER2 drugs. According to data available so far, these combinations did not result in additional aggravation of CV side effects.[23] Yet, results of a large prospective randomized study (Aphinity) investigating a combination of pertuzumab and trastuzumab as adjuvant therapy are expecting to shed more light on the issue.[24] Another two studies of neoadjuvant therapy (Neosphere and Tryphaena) showed better results in women with breast cancer treated with chemotherapy and dual HER2 blockade (pertuzumab and trastuzumab) as compared with patients treated with chemotherapy and trastuzumab alone. In the Tryphaena study, the primary endpoint of CV safety with a low incidence of symptomatic and asymptomatic systolic LV dysfunction was achieved in all study groups.[25] Finally, it should be noted that the benefit of trastuzumab in terms of reducing the risk of the underlying malignant disease outweighs the increased risk of cardiotoxicity.

Bevacizumab

Bevacizumab je humanizirano protutijelo protiv faktora rasta vaskularnog endotela (VEGF) i rabi se u liječenju bolesnika s metastatskim karcinomom debeloga crijeva i dojke, karcinoma nemalih plućnih stanica, bubrežnih stanica, jajnika i glioblastomoma multiforme. Kardiotoksičnost se najčešće očituje u obliku nekontrolirane arterijske hipertenzije. Najteži, 3. i 4. stupanj arterijske hipertenzije pojavljuju se u 9,2 % bolesnika, a rijetki su slučajevi hipertenzivnih kriza, uključujući encefalopatije ili intrakranijalna krvarenja. Hipertenzija se razvija u bilo koje vrijeme tijekom liječenja, a neki podatci upućuju na to da postoji veza između veličine pojedine doze i nepovoljnih ishoda.[26,27] ZS se pojavljuje u 1,7 do 3 %, a mehanizam može biti povezan s nekontroliranom hipertenzijom i inhibicijom VEGF signalizacije.[28]

Pri terapiji bevacizumabom u oko 3,8 % bolesnika moguća je pojava fatalnih tromboembolijskih incidenata, kao što su infarkt miokarda, ishemijski cerebrovaskularni inzult i plućna embolija. Tromboembolijski se incidenti mogu pojaviti u bilo koje vrijeme od početka terapije, mehanizam njihova nastanka nije nejasan i nije povezan s pojedinačnom kao ni kumulativnom dozom. Rizik je veći u starijih bolesnika (≥ 65 godina) te u onih s anamnezom prethodnoga arterijskoga tromboembolijskog događaja.[29] Čini se da nastaje zbog utjecaja antitumorske terapije na koagulacijsku kaskadu uz oštećenje intime krvnih žila i kontinuiteta endotelnih stanica, a anti-VEGF terapija smanjuje razinu NO-a i prostaciklina, što pogoduje nastanku tromboembolija.[30]

Inhibitori tirozin-kinaze

TKI se također mogu podijeliti na blokatore HER2 puta, poput lapatiniba, te bilo na specifične, poput axitiniba, bilo na nespecifične (sunitinib, sorafenib, vandetanib i pazopanib) blokatore VEGF puta.

Lapatinib je TKI koji je učinkovit u liječenju HER2p95 (okrnjeni oblik HER2) pozitivnog raka dojke. Čini se da liječenje lapatinibom ima nisku učestalost ZS-a ili drugih štetnih KV učinaka.[31] U kliničkim je studijama tek u oko 1,6 % bolesnika EFLV smanjena za najmanje 20 %, a oko 0,2 % bolesnika imalo je simptomatsko ZS. Nadalje, učestalost kardiotoksičnih komplikacija povećana je u bolesnika koji su prethodno primali antracikline ili trastuzumab.[32] Također je u dijela bolesnika zabilježeno reverzibilno produljenje QT intervala. Preporučuje se redovito praćenje EKG-a, kao i prilagodba doze ili prekid liječenja u bolesnika s produljenjem QT intervala.

Sorafenib je TKI koji se uporabljuje u liječenju uznapredovanog raka bubrega i jetre te na radioaktivni jod rezistentnog uznapredovanog raka štitnjače. Pri liječenju sorafenibom najvažnija nuspojava jest hipertenzija koja se pojavljuje u 17 –43 % bolesnika.[33] Tijekom terapije sorafenibom opisana je pojava akutnoga koronarnog sindroma, a u 2,9 % bolesnika i infarkta miokarda. Toksičnost sorafeniba moguće je objasniti inhibicijom RAF1 koji inhibira proapoptotske kinaze. Pojava hipertenzije može se pripisati inhibiciji VEGF receptora koja uzrokuje smanjenje permeabilnosti kapilara i povećano volumno opterećenje.[34]

Sunitimib je TKI koji se upotrebljava u liječenju raka bubrega i gastrointestinalnoga stromalnog tumora (GIST), a djeluje

Bevacizumab

Bevacizumab is a humanized anti-VEGF antibody that is used in the treatment of patients with metastatic colon and breast cancer, non-small-cell lung carcinoma, renal cell and ovarian carcinoma, and glioblastoma multiforme. Bevacizumab cardiotoxicity generally manifests in the form of uncontrolled arterial hypertension. The most severe grade 3 and 4 arterial hypertension occurs in 9.2% of patients, with rare cases of hypertensive crisis including encephalopathy or intracranial hemorrhage. Hypertension may develop at any time during bevacizumab therapy, with some data suggesting an association of individual dose size and unfavorable outcomes.[26,27] The mechanism of HF that occurs in 1.7%-3.0% of cases may be related to uncontrolled hypertension and inhibition of VEGF signaling.[28]

Fatal thromboembolic events such as myocardial infarction, ischemic stroke and pulmonary embolism may occur in 3.8% of patients on bevacizumab therapy. Thromboembolic events can occur at any time from therapy initiation. The mechanism of their occurrence remains obscure and does not appear to be related to either individual or cumulative drug dose. The risk is higher in elderly patients (age ≥65) and in those with a history of arterial thromboembolic event.[29] It is speculated that these events are induced by the antitumor therapy effect on the coagulation cascade with vascular intimal and endothelial cell continuity impairment, while anti-VEGF therapy reduces nitric oxide and prostacyclin levels, thus favoring development of thromboembolism.[30]

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors can also be classified into HER2 pathway blockers such as lapatinib, and specific (axitinib) or nonspecific (sunitinib, sorafenib, vandetanib and pazopanib) VEGF pathway inhibitors.

Lapatinib is a TKI efficacious in the treatment of HER2p95 (aberrant form of HER2) positive breast cancer. It appears that lapatinib therapy is associated with a low prevalence of HF or other adverse CV effects.[31] In clinical studies, LVEF reduced by at least 20% was recorded in only 1.6% and symptomatic HF in 0.2% of patients. The prevalence of cardiotoxic complications was increased in patients having previously received anthracyclines or trastuzumab[32]. In addition, reversible QT interval prolongation was recorded in some patients. In these patients, regular electrocardiographic (ECG) follow up along with dose adjustment or therapy discontinuation is recommended.

Sorafenib is a TKI used in the treatment of advanced renal cell and hepatocellular carcinoma, and advanced radioactive iodine-refractory thyroid carcinoma. Hypertension is the major side effect of sorafenib therapy, recorded in 17%-43% of cases.[33] Sorafenib therapy has been reported to be associated with development of acute coronary syndrome and of myocardial infarction in 2.9% of patients. Sorafenib toxicity can be explained by the inhibition of RAF1, which inhibits proapoptotic kinases. The occurrence of hypertension can be attributed to the VEGF receptor inhibition, which leads to reduced capillary permeability and increased volume load.[34]

Sunitinib is a TKI used in the treatment of renal cell carcinoma and gastrointestinal stromal tumor. Sunitinib acts on

na proliferaciju tumorskih stanica tumora, kao i na tumorsku angiogenezu.[35] U znatnog udjela (oko 47 %) bolesnika liječenih sunitinibom razvija se hipertenzija, dok se u 11 % bolesnika razvio KV događaj, uključujući i akutni infarkt miokarda i ZS. Asimptomatsko smanjenje EFLV-a od najmanje 10 % zabilježeno je u gotovo 28 % bolesnika.[36] Srednje vrijeme do razvoja ZS-a kreće se u rasponu od 22 dana do 27 tjedana, ali se čini da dobro reagira na farmakološko liječenje. Posebno su rizični bolesnici s anamnestičkim podatkom o koronarnoj bolesti srca, ZS-u, disfunkciji LV-a i prethodnoj terapiji antraciklinima. Sam mehanizma nastanka kardiotoksičnosti nije poznat, a najvjerojatnije nastaje zbog sunitimibom uzrokovane inhibicije niza receptora faktora rasta u kardiomiocitima.[37]

Ipilimumab, Nivolumab, Pembrolizumab

Protutijela za modulaciju imunosnog odgovora pokazala su se učinkovitima u liječenju više tipova tumora, uključujući melanom (anti-CTLA-4 i PD-1), rak nemalih plućnih stanica (NSCLC) te karcinoma bubrežnih stanica (RCC). Međutim, liječenje uzrokuje i mnoštvo imunosno posredovanih nuspojava, uključujući za sada ipak pojedinačne slučajeve miokarditisa i/ili perikarditisa.[38]

Praćenje bolesnika koji se liječe biološkom antitumorskom terapijom

U svih onkoloških bolesnika u kojih se planira biološka terapija potencijalno kardiotoksičnim lijekovima potrebno je učiniti detaljnu KV procjenu, no ipak će se samo u manjeg dijela bolesnika razviti KV komplikacije. Stoga je potrebno rano prepoznati i pratiti bolesnike s visokim rizikom. U svih je bolesnika prije i tijekom liječenja potrebno obaviti klinički pregled i elektrokardiogram (EKG). Otkrivanje bilo kakvih abnormalnosti u EKG-u poput tahikardije u mirovanju, promjena ST-T segmenta, smetnji provođenja, produljenje QT-intervala ili aritmije može upozoriti na kardiotoksičnost. Transtorakalna ehokardiografija osnovna je dijagnostička metodu za procjenu funkcije LV-a i preporučuje se učiniti je prije početka liječenja, u tromjesečnim intervalima tijekom te nakon završetka liječenja kardiotoksičnom terapijom. Procjena funkcije LV-a posebno je bitna kod anti-HER terapije, gdje je većina bolesnika prije početka ciljanog liječenja primala antracikline te je iznimno važno procijeniti funkciju LV-a nakon prethodne kemoterapije, a prije započinjanja ciljanog liječenja.[39] Funkcija LV-a procjenjuje se dvodimenzijskom (Simpsonovom) metodom, a, ako je dostupna, moguće je to učiniti i 3D ehokardiografijom.[40] Ostale novije ehokardiografske tehnike poput kontrastne ehokardiografije i stresne ehokardiografije indicirane su za procjenu graničnih standardnih ehokardiografskih nalaza. Tkivni dopler i analize deformacije korisni su za rano otkrivanje disfunkcije LV-a i treba ih primjenjivati kada god je moguće, a posebno je korisna procjena globalne uzdužne sistoličke deformacije (eng. *Global Longitudinal Strain*) čije je smanjenje od 15 % rani znak sistoličke disfunkcije.[41] Terapija se prekida ili privremeno obustavlja ako se EFLV smanji za 15 – 16 % od početne ili za 10 – 15% od normale. Ako nakon četiri tjedna ne nastupi poboljšanje EFLV-a, preporučuje se obustaviti ciljanu terapiju. Praćenje srčanih biokemijskih biljega

tumor cell proliferation and tumor angiogenesis.[35] Hypertension develops in a substantial proportion of sunitinib treated patients (47%), while 11% of patients experience CV events including acute myocardial infarction and HF. Asymptomatic LVEF reduction by at least 10% was recorded in nearly 28% of patients.[36] The mean time to HF development is 22-27 days; however, it appears to respond well to medical therapy. High-risk patients are those with a history of coronary disease, HF, LV dysfunction and previous anthracycline therapy. The true mechanism of cardiotoxicity remains unknown; however, it is most likely induced by inhibition of a series of growth factor receptors in cardiomyocytes.[37]

Ipilimumab, Nivolumab and Pembrolizumab

Antibodies for immune response modulation have proved efficacious in the treatment of various tumor types including melanoma (anti-CTLA-4 and PD-1), non-small-cell lung carcinoma and renal cell carcinoma. However, this therapy leads to a number of immune mediated side effects, so far including occasional cases of myocarditis and/or pericarditis.[38]

Follow up in Patients on Antitumor Biological Therapy

Thorough CV evaluation must be performed in all oncologic patients planned to be administered biological therapy with potentially cardiotoxic agents; yet CV complications will only develop in a minor proportion of patients. Therefore, it is of utmost importance to early identify and follow-up patients at high risk. All patients should undergo clinical examination and ECG before and during treatment. Detecting any ECG abnormalities such as tachycardia at rest, ST-T segment changes, conductivity impairment, QT-interval prolongation or arrhythmia may point to cardiotoxicity. Transthoracic echocardiography is the main diagnostic method for LV function assessment; it is recommended to perform it prior to therapy initiation, then at 3-month intervals, and upon completion of cardiotoxic therapy. Evaluation of LV function is crucial in anti-HER therapy since the majority of patients had received anthracyclines prior to targeted therapy introduction; it is of utmost importance to assess LV function after previous chemotherapy and before targeted therapy initiation.[39] LV function is assessed by two-dimensional (2D, Simson) method or by 3D echocardiography if available.[40] Other novel echocardiography techniques such as contrast echocardiography and stress echocardiography are indicated for assessment of borderline standard echocardiography findings. Tissue Doppler imaging and strain analysis are useful in early detection of LV dysfunction and should be used whenever possible. Assessment of the global longitudinal systolic strain is highly useful, as its reduction to less than 15% is an early sign of systolic dysfunction.[41] Therapy is suspended or temporarily discontinued in case of LVEF 15%-16% reduction from baseline or 10%-15% reduction from normal. Discontinuation of targeted therapy is recommended if LVEF fails to recover within 4 weeks. Monitoring cardiac biochemical markers (troponin and natriuretic peptides) during cardiotoxic therapy can help detect an early myocardial lesion. However, elevated levels of

(troponin, natriuretski peptidi) korisno je u vrijeme kardiotoksične terapije kako bi se otkrilo rano oštećenje miokarda. Međutim, povišene vrijednosti biokemijskih biljega samo detektiraju bolesnike s visokim rizikom za razvoj kardiotoksičnosti jer za sada nema jasnih dokaza da je kod patološkog nalaza potrebno prekinuti ili obustaviti onkološku terapiju.[42]

Liječenje kardiotoksičnosti inducirane anti-HER2 terapijom ne razlikuje se od liječenja drugih bolesnika sa ZS-om i u osnovi se rabe inhibitori ACE i beta-blokatori, a u slučaju simptomatskog ZS-a, i diuretici.[43] U bolesnika liječenih blokatorima VEGF signalnog puta potrebni su pažljiva procjena KV čimbenika rizika na početku, redovita kontrola arterijskoga tlaka i rano uvođenje antihipertenzivne terapije. U većine je bolesnika nakon regulacije arterijskog tlaka bilo moguće nastaviti anti-VEGF terapiju.[44]

Zaključak

Onkološki bolesnici koji primaju biološku ciljanu terapiju s povećanim rizikom od pojave kardiotoksičnosti zahtijevaju multidisciplinarni pristup i redovito kardiološko praćenje kako bi se navrijeme prepoznale i adekvatno liječile KV nuspojave. Na taj se način postiže poboljšanje kliničkih ishoda i kvalitete života te, ako je moguć, i optimalni nastavak specifičnoga onkološkog liječenja.

biochemical markers can only identify patients at high risk of cardiotoxicity because for the time being, there is no clear evidence that oncologic therapy should be suspended or discontinued in case of their pathologic finding.[42]

Treatment of anti-HER2 therapy induced cardiotoxicity does not differ from treatment of other HF patients; generally, angiotensin-converting enzyme inhibitors (ACEi) and beta-blockers are used, along with diuretics in case of symptomatic HF.[43] In patients administered VEGF signal pathway blockers, careful assessment of CV risk factors is required at therapy initiation, followed by regular blood pressure follow up and early introduction of antihypertensive therapy. In most patients, anti-VEGF therapy can be continued upon proper blood pressure regulation.[44]

Conclusion

Oncologic patients receiving targeted biological therapy associated with a high risk of cardiotoxicity require multidisciplinary approach and regular cardiologic follow up for timely recognition and appropriate treatment of CV side effects. Such an approach results in more favorable clinical outcomes and patient quality of life, along with optimal continuation of specific oncologic treatment if possible.

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