Kardiovaskularna toksičnost uzrokovana onkološkim liječenjem

Cardiovascular toxicity caused by oncological treatment

Ivo Darko Gabrić[1,2]*

[1]Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska

[2]Hrvatsko katoličko sveučilište, Medicinski fakultet, Zagreb, Hrvatska

[1]University Hospital Centre "Sestre milosrdnice", Zagreb, Croatia

[2]Catholic University of Croatia, School of Medicine, Zagreb, Croatia

RECEIVED: November 5, 2023

ACCEPTED: November 15, 2023

CITATION: Cardiol Croat. 2024;19(3-4):166-8. | https://doi.org/10.15836/ccar2024.166

***ADDRESS FOR CORRESPONDENCE**: Ivo Darko Gabrić, Klinički bolnički centar Sestre milosrdnice, Vinogradska 29, HR-10000 Zagreb, Croatia. / Phone: +385-91-5315-990 / E-mail: idgabric@gmail.com

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

TO CITE THIS ARTICLE: Gabrić ID. Cardiovascular toxicity caused by oncological treatment. Cardiol Croat. 2024;19(3-4):166-8.| https://doi.org/10.15836/ccar2024.166

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2024.166

U proteklih 20-ak godina preživljenje bolesnika s malignim bolestima produljilo se napredovanjem kemoterapijskih protokola, uvođenjem ciljanoga biološkog liječenja, poboljšanjem kirurgije, radioterapije, kao i novih metoda interventne radiologije[1]. Čak se i pojedine metastatske bolesti mogu dugoročno kontrolirati, čime praktički postaju kronične. Poboljšanje preživljenja, međutim, često je na štetu oštećenja drugih organa, uključujući i kardiovaskularni (KV) sustav[2], a danas su KV bolesti drugi vodeći uzrok dugoročnog pobola i smrtnosti među bolesnicima liječenima zbog karcinoma.[3]

U početku je pojava kardiotoksičnosti bila gotovo isključivo povezana s razvojem ireverzibilne sistoličke disfunkcije lijeve klijetke (LK) sve do simptomatskog zatajivanja srca zbog antraciklinske terapije. Pojavom biološke anti-HER terapije, utvrđeno je da ona može uzrokovati većim dijelom reverzibilno oštećenja srčane funkcije. To je prije 15 godina dovelo do podjele kardiotoksičnosti na dva osnovna tipa: ireverzibilni (tip I.) i reverzibilni (tip II.)[4], međutim, zbog mnogo preklapanja i kliničke slike i tijeka bolesti ta se podjela na dva tipa nije pokazala jednoznačnom i sveobuhvatnom. S druge strane, kardiotoksičnost se ne može povezati samo sa sistoličkom disfunkcijom LK-a jer onkološka terapija može uzrokovati niz KV bolesti poput novonastale ili pogoršane hipertenzije, vazospastičke i/ili trombotske ishemije miokarda, pogoršanja ateroskleroze, poremećaja ritma i provođenja te miokarditisa. Bitno je odrediti i osobe visokog rizika za razvoj kardiotoksičnosti, a predispozicija je multifaktorska te određena interakcijom genskih i okolišnih čimbenika. Neki od definiranih čimbenika rizika jesu na KV bolesti pozitivna obiteljska anamneza, dob, spol, arterijska hiper-

In the past 20 years or so, the survival of patients with malignant diseases has been prolonged due to the improved chemotherapy protocols, targeted biological treatment, enhanced surgery and radiotherapy and new interventional radiology methods[1]. Nonetheless, certain metastatic diseases can be managed in the long term, making them practically chronic. However, improvement in survival is often at the expense of damage to other organs, including the cardiovascular (CV) system[2]. CV diseases are the second leading cause of long-term morbidity and mortality in patients treated for cancer[3].

Initially, the occurrence of cardiotoxicity was almost exclusively associated with the anthracycline therapy induced irreversible left ventricular (LV) systolic dysfunction leading to symptomatic heart failure. With the development of biological anti-HER based therapy, it has been established that it can cause, for the most part, reversible damage of heart function. A decade and half ago, this triggered a division of cardiotoxicity into two basic types: irreversible (type I) and reversible (type II)[4]. However, due to a substantial amount of overlapping in terms of both the clinical picture and the course of the disease, this division has not demonstrated to be indisputable and comprehensive. On the other hand, cardiotoxicity cannot be associated only with LV systolic dysfunction as oncology therapy may cause a number of CV diseases such as new or worsening hypertension, vasospastic and/or thrombotic ischemia in the myocardium, worsening of atherosclerosis, rhythm and conduction disorders, and myocarditis. It is also important to identify patients at high risk for developing cardiotoxicity; the predisposition is multifactorial and determined by an interaction of genetic and

tenzija i dislipidemija. Također je utvrđeno da postoji povećan rizik od razvoja kardiotoksičnosti u bolesnika sa smanjenom sistoličkom funkcijom LK te značajnim aritmijama.[5] Osim toga, bilo je potrebno definirati praćenje bolesnika koji primaju ili su primili kardiotoksičnu kemoterapiju. Naime, kardiotoksičnost se može simptomatski ili potpuno asimptomatski manifestirati tijekom ili neposredno nakon liječenja (u nekoliko dana ili tjedana), ali i dulje vrijeme nakon završetka antitumorske terapije (npr. nakon primjene antraciklina).[6] Zbog složenosti bolesti pojavila se potreba formiranja kardioonkoloških timova.

U skladu sa svim navedenim jasno je da je postojala potreba izradbe smjernica iz kardioonkologije. Stoga je Europsko kardiološko društvo, nakon što je 2016. izdalo *Position Paper*[7], pristupilo izradbi sveobuhvatnih smjernica koje su objavljene 2022. godine.[8] Smjernice su uzele u obzir sve aspekte kardioonkologije tako da se i umjesto starog izraza kardiotoksičnost u njima rabi novi izraz **kardiovaskularna toksičnost povezana s onkološkom terapijom** (CTR-CVT). One također donose nove standarde za definiranje KV toksičnosti povezane s onkološkom terapijom, te protokole za nadzor nad bolesnikom tijekom i nakon onkološkog liječenja, dijagnostiku i liječenje CRT-CVT-a. Osim šest osnovnih patofizioloških mehanizama za razvoj CRT-CVT-a, navedene su i iznimke KV toksičnosti koje mogu uzrokovati pojedini onkološki lijekovi. Naglasak je na prevenciji, odnosno procjeni rizika za razvoj KV toksičnosti prije primjene onkološke terapije, čime se minimalizira nepotrebno prekidanje onkološkog liječenja. Cijelo vrijeme treba imati na umu da svaki prekid ili promjena onkološkog liječenja može znatno promijeniti ishode onkološkog liječenja i prognozu bolesti. Pristup CRT-CVT-u mora biti multidisciplinaran te se preporučuje razvoj kardioonkoloških supspecijalista koji bi imali široko znanje o kardiologiji, onkologiji i hematologiji. Najveći nedostatak smjernica jest u tome što većina preporuka proizlazi iz mišljenja stručnjaka ili registara (razina dokaza C). Jednostavno, nemoguće je napraviti dovoljno randomiziranih kliničkih pokusa.

U ovom broju časopisa *Cardiologia Croatica* u objavljenom radu Czuriga *i sur.*[9] naveden je razvoj definicije KV toksičnosti, s posebnim osvrtom na prve Kardioonkološke smjernice Europskoga kardiološkog društva. Kao opći cilj navedeno je da se bolesnicima osigura najbolja moguća onkološka terapija na siguran način, a da se CTR-CVT svede na minimum. To bi minimaliziralo nepotrebno prekidanje terapije. Autori su također ukratko predstavili ključni *CARDIOTOX* registar.

Sve se više bolesnika liječi kemoterapijom i biološkim lijekovima tako da se incidencija KV toksičnosti neprestano povećava.[10] Opseg problema još je veći jer dio bolesnika mora uzimati kombinaciju više kardiotoksičnih lijekova.[11] Onkološki bolesnici s povećanim rizikom od pojave KV toksičnosti zahtijevaju multidisciplinaran pristup i redovito kardiološko praćenje kako bi se navrijeme prepoznale i adekvatno liječile nuspojave. Na taj se način postiže poboljšanje kliničkih ishoda i kvalitete života, a, ako je moguć, i optimalan nastavak specifičnoga onkološkog liječenja.

environmental factors. Some of the defined risk factors are a positive family history of CV disease, age, gender, arterial hypertension and dyslipidemia. It has also been established that there is an increased risk for the development of cardiotoxicity in patients with reduced LV systolic function and significant arrhythmias.[5] In addition, it was necessary to define the follow-up of patients currently receiving or who had previously received cardiotoxic chemotherapy. Cardiotoxicity can manifest itself symptomatically or completely asymptomatically during or immediately after treatment (in the following few days or weeks), but also long time after the end of antitumor therapy (e.g. after the use of anthracyclines).[6] Due to the complexity of the disease, it was necessary to form cardio-oncology teams.

All of the above demonstrates a need to develop guidelines in cardio-oncology. For that reason, after issuing *Position Paper*[7] in 2016, the European Society of Cardiology (ESC) started to develop comprehensive guidelines that were published in 2022[8]. The guidelines took into account all aspects of cardio-oncology, so instead of the old term cardiotoxicity, a new term **cancer therapy-related cardiovascular toxicity** (CTR-CVT) is used. The guidelines also introduce new standards for defining CV toxicity associated with oncology therapy, and protocols for monitoring patients during and after oncology treatment, diagnosis and treatment of CRT-CVT. In addition to the 6 basic pathophysiological mechanisms for the development of CRT-CVT, the exceptions of CV toxicity that can be caused by certain oncological drugs are listed as well. The emphasis is on prevention, i.e. risk assessment for the development of cardiovascular toxicity before the application of oncology therapy, which minimizes the unnecessary interruption of oncology treatment. It should always be kept in mind that any interruption or change in oncological treatment can significantly change the results of oncological treatment and the prognosis of the disease. The CRT-CVT approach needs to be multidisciplinary, and the development of cardio-oncology subspecialists who have broad knowledge of cardiology, oncology and hematology is recommended. The major weakness of the guidelines is that most of the recommendations are derived from expert opinions or registries (evidence level C). It is simply impossible to do enough randomized clinical trials.

In this issue of *Cardiologia Croatica*, the paper published by Czuriga *et al.*[9] explains the development of the definition of CV toxicity with special reference to the first ESC guidelines on cardio-oncology. The general goal is to provide patients with the best possible oncology therapy in a safe manner, and to reduce CTR-CVT to a minimum. This would reduce unwanted disturbance of therapy. The authors also briefly presented the key CARDIOTOX registry.

An increasing number of patients are treated with chemotherapy and biological drugs, so the incidence of CV toxicity is continuously increasing.[10] The extent of the problem is even greater because some patients have to take a combination of several cardiotoxic drugs[11]. Oncology patients with an increased risk of CV toxicity require a multidisciplinary approach and regular cardiological monitoring in order to recognize and adequately treat side effects in a timely manner. In this way, the improvement of clinical outcomes and quality of life is achieved and, possibly, the optimal continuation of specific oncological treatment.

LITERATURE

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. https://doi.org/10.3322/caac.21660
2. Dent S, Liu P, Brezden-Masley C, Lenihan D. Cancer and Cardiovascular Disease: The Complex Labyrinth. J Oncol. 2015;2015:516450. https://doi.org/10.1155/2015/516450
3. Herrmann J, Lenihan D, Armenian S, Barac A, Blaes A, Cardinale D, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. Eur Heart J. 2022 Jan 31;43(4):280-299. https://doi.org/10.1093/eurheartj/ehab674
4. Bowles EJ, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T, et al; Pharmacovigilance Study Team. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst. 2012 Sep 5;104(17):1293-305. https://doi.org/10.1093/jnci/djs317
5. Deng S, Wojnowski L. Genotyping the risk of anthracycline-induced cardiotoxicity. Cardiovasc Toxicol. 2007;7(2):129-34. https://doi.org/10.1007/s12012-007-0024-2
6. Aleman BM, Moser EC, Nuver J, Suter TM, Maraldo MV, Specht L, et al. Cardiovascular disease after cancer therapy. EJC Suppl. 2014 Jun;12(1):18-28. https://doi.org/10.1016/j.ejcsup.2014.03.002
7. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016 Sep 21;37(36):2768-2801. https://doi.org/10.1093/eurheartj/ehw211
8. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al; ESC Scientific Document Group. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022 Nov 1;43(41):4229-4361. https://doi.org/10.1093/eurheartj/ehac244
9. Czuriga D, Drobni ZS, Pozsonyi Z. The evolution of defining and the reinterpretation of cardiotoxicity. Cardiol Croat. 2024;19(3-4):169-76. https://doi.org/10.15836/ccar2024.169
10. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail. 2020 Nov;22(11):1945-1960. https://doi.org/10.1002/ejhf.1920
11. van Kalsbeek RJ, Mulder RL, Skinner R, Kremer LCM. The Concept of Cancer Survivorship and Models for Long-Term Follow-Up. Front Horm Res. 2021;54:1-15. https://doi.org/10.1159/000514693