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Utjecaj kemoterapije na kardiovaskularni sustav

The impact of chemotherapy on the cardiovascular system

Renata Dobrila-Dintinjana[1], Marijan Dintinjana[2]

[1]Clinical Hospital Centre Rijeka, Rijeka

[2]General Practice Dr Dintinjana, Rijeka

***SAŽETAK**: Većina antineoplastičnih lijekova uzrokuje kardijalnu toksičnost. Akutna kardijalna toksičnost može onemogućiti provođenje daljnje kemoterapije. Antraciklini najčešće uzrokuju kardiotoksičnost i to unutar nekoliko dana od primjene lijeka pa sve do 25 godina nakon prestanka terapije. Kardiotoksičnost 5-fluorouracila se očituje kod 1,1% do 7,6% bolesnika. Najčešći su kardiospazam i srčano popuštanje. Interferoni uzrokuju aritmije do u 20% bolesnika, a trastuzumab pridonosi kardiotoksičnosti antraciklina. Bevacizumab i cetuximab su relativno prekratko u upotrebi da bi se mogla utvrditi tzv. kasna srčana toksičnost. Kod aplikacije kemoterapije, ne smijemo zaboraviti ni na potencijalnu kardiotoksičnost, tzv. suportivnih lijekova, npr. granisetrona. Svi bolesnici koji su primali kemoterapiju trebaju višegodišnje kardiološke kontrole.*

***KLJUČNE RIJEČI**: kardiotoksičnost, kemoterapija, monoklonalna antitijela*

***SUMMARY**: The majority of antineoplastic agents cause cardiac toxicity. Acute cardiac toxicity can prevent the administration of on-going chemotherapy. Anthracycline most often causes cardiotoxicity within a few days of administrating medication with effects lasting up to 25 years following the completion of therapy. Cardiotoxicity of 5-Fluorouracil is evident in between 1.1% and 7.6% of patients. Most frequent are cardiospasm and heart failure. Interpherones cause arrhythmia in up to 20% of patients, while trastuzumab contributes to anthracycline cardiotoxicity. Bevacizumab and cetuximab have been in use for a relatively a short time for determining so-called late cardiac toxicity. When applying chemotherapy, we must not forget about potential cardiotoxicity, so-called supportive medicines, e.g. granisetrone. All patients who have received chemotherapy should in years to come undergo heart check-ups.*

***KEYWORDS**: cardiotoxicity, chemotherapy, monoclonal antibodies*

Iako su solidni tumori i dalje bolesti pretežno starijih životnih skupina, sve je više djece-bolesnika te bolesnika u dvadesetim i ranim tridesetim godinama. Zahvaljujući napretku medicine i izumu novih lijekova vrijeme života bolesnika sa solidnim tumorima je značajno produženo, a određeni postotak preživljava dugi niz godina.

Mnogo antineoplastičnih lijekova uzrokuje kardijalnu toksičnost. Akutna kardijalna toksičnost važna je poradi akutnih komplikacija i nemogućnosti provođenja daljnje terapije, a i tzv. odložena kardijalna toksičnost postaje sve značajniji problem.

Antraciklini su lijekovi koji se najčešće dovode u vezu s kardiotoksičnošću. **Halazun** i **Van Hoff** su u ranim sedamdesetim godinama 20-tog stoljeća dokazali da je incidencija srčanog popuštanja i težina patološke lezije u linearnom odnosu s totalnom kumulativnom dozom lijeka[1-3]. Antraciklinska kardiomiopatija se prezentira kao akutna, subakutna i kasna. Akutna se javlja kao mioperikarditis unutar nekoliko dana od primjene lijeka, a rezultat je direktnog oštećenja srca antraciklinima i oštećenja kateholaminima i histaminom koji se pod utjecajem kemoterapije pojačano luče. Aritmije, perikardijalni izljev i srčano popuštanje su najznačajnije manifestacije, smrt je rijetka. Subakutna toksičnost se javlja od 0-tog do 270-tog dana (najčešće oko trećeg mjeseca) po aplikaciji antraciklina i to sa znacima kongestivnog srčanog popuštanja[1-3]. Danas bolesnici uglavnom povoljno reagiraju na konzervativnu terapiju, a u ranije publiciranim studijama smrtnost je bila velika, do 60%. Gubitak miocita i miocitna nekroza glavni su patološki nalazi[1-3].

Kasna prezentacija antraciklinske kardiomiopatije odnosi se na bolesnike koji razviju srčano popuštanje 5 do 25

Even though solid tumours continue to be illnesses affecting people of an older age group, an increasing number of patients are affected such as children and those in their twenties and early-thirties. Thanks to the advancement and discoveries of new medicines, the lifetime of a patient with solid tumours has been significantly extended, while a certain percentage of them live on for many years.

Many antineoplastic agents cause cardiac toxicity. Acute cardiac toxicity is an important issue due to acute complications and prevention in administering further therapy, while so-called delayed cardiac toxicity is becoming an increasing problem.

Anthracyclines are medicines relating most often to cardiotoxicity. **Halazun** and **Van Hoff** in the early 1907s showed that the incidents of heart failure and the degree of pathological lesions are linearly related to the total cumulative dose of medication[1-3]. Anthracycline cardiomyopathy appears as acute, subacute and late. Acute appears as myopericarditis within a few days of receiving the medication, resulting in direct damage to the heart due to anthracyclines and including catecholamines and histamines which under the effect of chemotherapy are released in even more. Arrhythmia, pericardial bleeding and heart failure are the most significant manifestations, whereas death is rare. Subacute toxicity appears from 0 up to 270 days (mostly around the third month) following administration of anthracycline along with signs of congestive heart failure[1-3]. Today, patients mostly favourably react to conservative therapy, while in earlier published studies death was common in up to 60% of cases. Loss of myocytes and myocyte necrosis are common pathological findings[1-3].

Later appearance of anthracycline cardiomyopathy is linked to patients developing heart failure within 5 to 25

godina nakon završetka terapije. Smanjena tolerancija u naporu, ozbiljne aritmije i smetnje provođenja su najčešća manifestacija bolesti[1,3]. Bolest može biti i asimptomatska te stoga svi bolesnici koji su primali antracikline trebaju dugogodišnji kardiološki nadzor, a pojavu aritmija ili sinkopa u tih bolesnika treba shvatiti kao ominozan znak koji zahtijeva brzu i detaljnu obradu[2].

Paclitaxel (skupina taxana) je lijek koji izaziva abnormalnosti kardijalnog ritma, provodnje i funkcije. U bolesnica s ovarijalnim karcinomom u prekliničkoj studiji faze II, uzrokovao je signifikantnu sinusnu bradikardiju u 29% bolesnica[4]. Opisuju se i AV blokovi I, II i III stupnja te asistolija za vrijeme kontinuirane infuzije lijeka[4]. Kombinacija paclitaxela s doxorubicinom koja se koristi za liječenje karcinoma dojke dovodi do klinički signifikantnog pogoršanja funkcije lijevog ventrikla[4,5].

Kardiotoksičnost 5-fluorouracila (5FU) uočena je već 1975. godine. Kroz sljedećih dvadeset godina u studijama kardiotoksičnost 5FU kretala se od 1,1% do 7,6%[6,7]. Kontinuirana infuzija 5FU je toksičnija od bolusa. Kardiotoksičnost se očituje kao: prekordijalna bol (nespecifična i anginozna); ST-T promjene na EKG-u (nespecifične i ishemijske); akutni infarkt miokarda (rijetko); atrijalne aritmije; ventrikularna disfunkcija, srčano popuštanje i iznenadna srčana smrt (rijetko)[6,7]. Dokazano je da se navedene promjene javljaju i u bolesnika s urednim koronarnim arterijama te se u njih najvjerojatnije radi o koronarnom vazospazmu[8]. Mehanizam nastanka ventrikularne disfunkcije i srčanog popuštanja nije potpuno jasan[6,7].

Iako rijetke, tromboze cerebralnih, koronarnih i arterija ekstremiteta mogu biti uzrokovane kemoterapijom i u odsutnosti vidljive tumorske bolesti[6,7]. Cisplatin i tamoxifen imaju veći postotak takvih pojava od drugih kemoterapeutika. Bleomycin i cisplatin u kombinaciji (ali i bleomycin sam) uzrokuju Raynaudov fenomen u 40% bolesnika. Bolni prsti i parestezije zaostaju godinama nakon završetka primjene lijekova[6,7].

U 15 kliničkih studija kardiotoksičnost interferona α, α2, β i γ bila je oko 10%; signifikantne abnormalnosti provodnje i ritma, ishemija i kardiomiopatija bile su najzapaženije promjene[9,10]. Toksične promjene se najčešće javljaju od 1 do 30-tog dana primjene lijeka, a ne ovise o dobi bolesnika, individualnoj i kumulativnoj dozi lijeka. Ishemijske promjene i rijetko infarkt miokarda mogu se javiti u bolesnika s predležećom ishemičnom bolesti srca. Aritmije se javljaju do u 20% bolesnika, i to svi oblici uključujući i fatalnu ventrikularnu fibrilaciju[9,10].

Trastuzumab (Herceptin) humanizirano monoklonalno antitijelo za HER2 receptore dovodi se u vezu sa slabljenjem sistoličke funkcije ali pretežito u bolesnika koji su ranije primali antracikline ili koji zajedno s transtuzumabom primaju antracikline[7,11]. Studije pokazuju da je kardiotoksičnost kombinacije trastuzumab+doxorubicin 4 puta veća nego kardiotoksičnost samog doxorubicina (27% *vs.* 6%). Trastuzumab i paclitaxel u kombinaciji dovode do srčanog popuštanja u 11% bolesnika, dok sam paclitaxel u 1%[7,11].

Cetuximab (Erbitux) humanizirano monoklonalno antitijelo koje se veže za receptore epitelnog čimbenika rasta,

years following completion of therapy. Reduced tolerance during exertion, serious arrhythmia and hindrances in administration are the most frequent manifestations of the illness[1-3]. The illness may also be asymptomatic, therefore all patients who have received anthracycline should undergo long-term heart check-ups. The appearance of arrhythmia or syncope in such patients should be accepted as an ominous sign requiring quick and detailed analysis[2].

Paclitaxel (category of taxanes) is a medicine causing abnormal cardiac rhythm, flow and functioning. In female patients with ovarian carcinomas in the preclinical study phase II, it caused significant sinus bradicardia in 29% of cases[4]. The AV block I, II and III stage including asystolis during continual infusion of medicines is also described[4]. A combination of paclitaxel with doxorubicin used in treating breast carcinomas leads to a significant clinical deterioration in the functioning of the left ventricle[4,5].

Cardiotoxicity of 5-Fluorouracil (5FU) was first noticed back in 1975. Through the next twenty years of studies, cardiotoxicity 5FU was between 1.1% and 7.6%[6,7]. Continual infusion of 5FU is more toxic than a bolus. Cardiotoxicity is evident as: a precordial pain (non-specific and anginal); ST-T changes in ECG (non-specific and ischemic); acute myocardial infarction (rare); atrial arrhythmia; ventricular dysfunction, heart failure and unexpected heart death (rare)[6,7]. It has been shown that the stated changes also appear in patients with orderly coronary arteries, hence it is most likely that coronary vasospasm is the cause[8]. The mechanism for the occurrence of ventricular dysfunction and heart failure is not completely clear[6,7].

Even through rare, thrombosis of cerebral, coronary and artery extremities may be caused by chemotherapy even in the absence of visible signs of tumours[6,7]. Cisplatin and tamoxifen offer a greater chance of such effects than other chemotherapeutics. Bleomycin and cisplatin in combination (but also bleomycin on its own) cause Raynaud's phenomenon in 40% of patients. Pain in the fingers and paresthesia remain for years to come following administration of medication[6,7].

In 5 clinical studies, cardiotoxicity of interpherones α, α2, β and γ was around 10%; significant abnormalities in flow and rhythm, ischemia and cardiomyopathy were the most evident changes[9,10]. Toxic changes most often appear between 1 and 30 days of administration of the medication, and do not depend on age of patient, individual and cumulative doses of medication. Ishemic changes and rarely myocardial infarction may also appear in patients with inherent ischemic heart disease. Arrhythmia appears in 20% of patients, and in all forms including fatal ventricular fibrillation[9,10].

Trastuzumab (Herceptin) humanized monoclonal antibodies for HER2 receptors is thought to be linked to the weakening of systolic functions but mostly in patients who had earlier received anthracycline or who together with transuzumab also receive anthracycline[7,11]. Studies have shown that cardiotoxicity combined with trastuzumab+doxorubicin is four times greater than the cardiotoxicity of doxorubicin (27% *vs.* 6%) itself. Trastuzumab in combination with paclitaxel leads to heart failure in 11% of patients, while paclitaxel on its own in only 1% of cases[7,11].

Cetuximab (Erbitux) humanized monoclonal antibodies linked to receptors with epithelial growth factor, caused

izazvao je kardiorespiratorni arest i iznenadnu smrt u 2% bolesnika u jednoj studiji[12,13]. Srčano popuštanje, ishemijske promjene, hipotenzija, bradikardija i EKG promjene (prolongacija QT-intervala) javljaju se u 2-3% bolesnika[12,13].

Bevacizumab (Avastin) je također humanizirano monoklonalno antitijelo za vaskularni čimbenik rasta. Izaziva srčano popuštanje i sinkope u 3% bolesnika, a u istom postotku i tromboembolijske incidente[13,14]. Studija u kojoj su se kombinirali bevacizumab i doxorubicin imala je kardiotoksičnost u 12% slučajeva (slično kao i kod monoterapije doxorubicinom), što je dokazalo da bevacizumab ne potencira kardiotoksičnost drugih kemoterapeutika[14].

Bevacizumab i cetuximab su relativno novi lijekovi koji se koriste za liječenje metastatskog kolorektalnog karcinoma. Izmjenom kemoterapeutskih protokola u kombinaciji s monoklonalnim antitijelima u visokom postotku dolazi do dužeg preživljavanja bolesnika, a vjeruje se i u zalječenje. Navedene terapije koriste se mjesecima pa i godinama. S obzirom na navedeno, moguće je da će se određena kardiotoksičnost pokazati i u kasnijem razdoblju (desetak godina i više nakon primjene tih lijekova) kod tzv. "dugih preživljavaoca".

Ne smijemo zaboraviti ni na kardiotoksičnost ostalih lijekova koje dobijaju onkološki bolesnici. Npr. antiemetik granisetron dovodi do sinusne bradikardije i AV blokova, a citokini i čimbenik stimulacije granulocita uzrokuju perikardijalni izljev[15].

Svakog bolesnika koji prima kemoterapiju neovisno o dobi, spolu i apliciranom lijeku potrebno je brižljivo monitorirati i pratiti kardijalnu funkciju. Bolesnicima kojima planiramo aplicirati kardiotoksičnu kemoterapiju potrebno je učiniti osnovnu kardiološku obradu (adekvatan pregled, EKG, ehokardiografski pregled srca). Tijekom liječenja nužno je tragati za potencijalnim kardiotoksičnim promjenama, vršiti redovne fizikalne preglede i snimati EKG. U slučaju sumnje na kardiotoksičnost, potrebno je proširiti kardiološku obradu i prekinuti liječenje.

cardiorespitory arrest and unexpected death in 2% of patients in one particular study[12,13]. Heart failure, ischemic changes, hypotension, bradycardia and ECG changes (QT-interval prolongations) appear in 2-3% of patients[12,13].

Bevacizumab (Avastin) is also a humanized monoclonal antibody for vascular growth factor. It causes heart failure and syncope in 3% of patients, as do thromboembolic incidents[13,14]. Studies where bevacizumab and doxorubicin were combined led to cardiotoxicity in 12% of cases (similar to doxorubicin monotherapy), suggesting that bevacizumab does not cause cardiotoxicity in other chemotherapeutics[13,14].

Bevacizumab and cetuximab are relatively new medicines used to treat metastatic colorectal carcinomas. Changing the chemotherapeutic protocols in combination with monoclonal antibodies in a high percentage of cases leads to longer survival periods for patients, and there is also a chance of healing. The stated therapy is to be in use for months and years, as well. Taking into consideration what has been said, it is possible that a certain cardiotoxicity will appear later in life (10 years and more following administration of the medication) with so-called "long-term survivors".

We must not forget about the cardiotoxicity in other medicines received by oncological patients. For instance, antiemetic granisetron leads to sinus bradycardia and AV blocks, while cytokinins and the granulocyte stimulation factor lead to pericardial effusion[15].

Any patient receiving chemotherapy regardless of age, sex or administered medicine, should be carefully monitored and their cardiac functioning analyzed. Patients who are expected to receive cardiotoxic chemotherapy should undergo basic cardiological analysis (adequate check-up, ECG, echocardiography). During treatment, it is necessary to search for potential cardiotoxic changes, complete regular physical check-ups and have ECGs performed. In the case of suspecting cardiotoxicity, it is necessary to expand cariodological analysis and cease treatment.

E-mail: marijan.dintinjana@ri.t-com.hr
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