KARDIOTOKSIČNOST ANTINEOPLASTIČNE TERAPIJE – MEHANIZMI NASTANKA, KLINIČNE MANIFESTACIJE I OSNOVNI POSTULATI KARDIO-ONKOLOGIJE

PREGLEDNI RAD

REVIEW ARTICLE

CARDIOTOXICITY OF ANTINEOPLASTIC THERAPY – UNDERLYING MECHANISMS, CLINICAL MANIFESTATIONS, AND BASIC PRINCIPLES OF CARDIO-ONCOLOGY

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SAŽETAK

Maligne bolesti i kardiovaskularne bolesti su najčešći uzroci morbiditeta i mortaliteta savremenog sveta. Uzimajući u obzir starenje populacije razvijenih zemalja i činjenicu da su maligne bolesti uglavnom bolesti starijeg životnog doba, projektovani porast broja obolelih u zemljama Evropske unije, do 2040. godine, iznosi preko 20%. Savremena, personalizovana terapija malignih bolesti, koja je značajno poboljšala prognozu i preživljavanje hemato-onkoloških bolesnika, podrazumeva i njihovo brižljivo ambulantno praćenje, kako bi se prevenirali, pravovremeno dijagnostikovali i adekvatno lečili neposredni i kasni neželjeni efekti antineoplastične terapije. Kardiovaskularni sistem je, s obzirom na specifičnost građe i funkcije, posebno osetljiv na antineoplastične agense. Personalizovani i multidisciplinarni pristup u lečenju i praćenju hemato-onkoloških bolesnika je doveo do razvoja nove subspecijalnosti – kardio-onkologije, čiji je osnovni zadatak rano identifikovanje onkoloških bolesnika, sa ili bez pridruženih kardiovaskularnih bolesti, koji imaju povećani rizik od nastanka kardiotoksičnosti uzrokovane hemato-onkološkom terapijom. U radu su navedeni osnovni mehanizmi kardiotoksičnosti najvažnijih grupa antineoplastičnih lekova, kliničke manifestacije, kao i savremene preporuke za primarnu i sekundarnu prevenciju.

Ključne reči: antineoplastični agensi, kardiotoksičnost, prevencija, lečenje

ABSTRACT

Malignancies and cardiovascular diseases are the most common cause of morbidity and mortality in the modern world. Taking into account the ageing population of developed countries and the fact that malignancies are mainly diseases of old age, the projected increase in the incidence of malignancies in the countries of the European Union, by 2040, is more than 20%. Modern, personalized therapy of malignant diseases, which has significantly improved the prognosis and survival of hemato-oncology patients, requires careful ambulatory patient follow-up, in order to prevent, timely diagnose and adequately treat the immediate and delayed adverse effects of antineoplastic therapy. The cardiovascular system is particularly sensitive to antineoplastic agents due to its particular structure and functions. A personalized and multidisciplinary approach in the treatment and follow-up of hemato-oncology patients has led to the development of a new subspeciality – cardio-oncology, whose main task is the early identification of oncological patients, with or without associated cardiovascular disease, who have an increased risk of developing cardiotoxicity during antineoplastic treatment. The article describes the basic mechanisms of cardiotoxicity of the most important groups of antineoplastic drugs, clinical manifestations as well as contemporary recommendations for primary and secondary prevention.

Keywords: antineoplastic agents, cardiotoxicity, prevention, treatment

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UVOD

Savremena terapija malignih bolesti značajno je poboljšala prognozu i preživljavanje hemato-onkoloških bolesnika [1]. U poslednjih četrdeset godina, desetogodišnje preživljavanje obolelih od ne-Hočkinovih limfoma poraslo je sa 20% na preko 65% [2]. I pored toga, maligne bolesti su vodeći uzrok prevremenog mortaliteta (smrtnost osoba mlađih od 70 godina) u razvijenim regionima sveta [3]. Uzimajući u obzir demografske promene, tj. starenje populacije razvijenih zemalja i činjenicu da su maligna oboljenja uglavnom bolesti starijeg životnog doba, projektovani porast broja obolelih u zemljama Evropske unije, do 2040. godine, iznosi preko 20% [4]. Kako stare osobe često imaju pridružene bolesti, odnosno komorbiditete, multidisciplinarni pristup lečenju, kao i poboljšanje kvaliteta života obolelih, predstavljaju osnovu Gerijatrijskog onkološkog programa koji sprovodi organizacija *EORTC* (engl. *European Organisation for Research and Treatment of Cancer*) [5].

INTRODUCTION

Modern treatment of malignant diseases has significantly improved the prognosis and survival of hemato-oncology patients [1]. In the past forty years, the ten-year survival of patients with non-Hodgkin lymphomas has increased from 20% to over 65% [2]. In addition, malignant diseases are the leading cause of premature mortality (death of people under 70 years of age) in developed regions of the world [3]. Taking into account demographic changes, i.e., the ageing of the population in developed countries, as well as the fact that malignant diseases are mostly diseases affecting the elderly, the projected increase in the number of patients in EU countries, by 2040, is over 20% [4]. As elderly people often have associated diseases, i.e., comorbidities, a multidisciplinary approach to treatment, as well as improving the quality of life of patients, are the basis of the Geriatric Oncology Program implemented by the European Organisation for Research and Treatment of Cancer (EORTC) [5].

Tabela 1. Klase antineoplastičnih lekova

Klasa	Podklasa	Lek
Alkilirajući agensi*	Azotni plikavci	Hlorambucil, Ciklofosfamid, Ifosfamid, bendamustin
	Derivati nitrozoureje	Karmustin, Fotemustin, Semustin, Lomustin, Streptozocin
	Triazeni	Dakarbazin
	Etilenamini i metilamini	Tiotepa
	Alkilsulfonati	Busulfan
	Epoksidi	Etoglucid
	Ostali	Temozolomid, Dakarbazin, Mitobronitol, Pipobroman
Antimetaboliti**	Analozi folne kiseline	Metotreksat, Pemetreksed, Raltitreksed
	Analozi purina	Azatioprin, Kladribin, Klofarabin, Fludarabin, Merkaptopurin, Nelarabin, Pentostatin, Tioguanin
	Analozi pirimidina	Doksifluridin, Fluorouracil, Uracil/Tegafur (UFT), Azacitidin, Kapecitabin, Citarabin, Decitabin, Gemcitabin
	Ostali	Hidroksiureja
Biljni alkaloidi i drugi prirodni produkti***	Vinka alkaloidi i analozi	Vinkristin, Vinblastin, Vindezin, Vinorelbin, Vinflunin, Vintafolid
	Inhibitori topoizomeraze I	Irinotekan, Topotekan, Belotekan
	Derivati podofilotoksina	Etopozid, Tenipozid
	Inhibitori kolhicina	Demekolcin
	Taksani	Docetaksel, Paklitaksel, Kabazitaksel
	Ostali	Trabektedin
Citotoksični antibiotici****	Aktinomicini	Daktinomicin
	Antraciklini	Aklarubicin, Daunorubicin, Doksorubicin, Epirubicin, Mitoksantron, Pirarubicin
	Ostali	Bleomicin, Mitomicin, Plikamicin

Objašnjenje: Mehanizam dejstva konvencionalnih citostatika –
*Alkilirajući agensi – Modifikuju strukturu DNK alkiliranjem nukleinskih baza (dodaju metil grupe na guanin i time onemogućavaju transkripciju i replikaciju DNK), deluju na sve ćelije u fazi deobe („ciklus-specifični"); ** Antimetaboliti – Strukturni analozi enzima koji učestvuju u sintezi DNK, specifični za S-fazu ćelijskog ciklusa; *** Biljni alkaloidi i drugi prirodni produkti – Sprečavaju polimerizaciju tubulina i sintezu mikrotubula deobnog vretena ili sprečavaju depolimerizaciju mikrotubula, zaustavljaju deobu ćelije u M-fazi ćelijskog ciklusa; **** Citotoksični antibiotici – Sprečavaju replikaciju direktnim dejstvom na DNA uzrokujući razdvajanje lanaca („ciklus-specifični").

Onkološko lečenje često podrazumeva istovremenu ili sukcesivnu primenu agenasa različitog mehanizma dejstva u cilju potenciranja antineoplastičnog efekta. Ciljana terapija monoklonskim antitelima (mAt), kao i malim molekulima, koji se primenjuju oralno, poput inhibitora tirozin kinaze, često podrazumeva kontinuirano lečenje do progresije bolesti [6]. U tabelama 1, 2, 3 i 4 su navedene najvažnije grupe antineoplastičnih lekova, prema klasifikaciji Svetske zdravstvene organizacije (dostupno na: https://www.whocc.no/atc_ddd_index/), i njihove mehanizme dejstva [7–11]. Savremeni pristup lečenju obolelih od malignih bolesti, sem personalizovane inovativne terapije koja značajno doprinosi uspehu, ali i skraćenju hospitalnog lečenja, podrazumeva i brižljivo ambulantno praćenje hemato-onkoloških bolesnika, kako bi se prevenirali, pravovremeno dijagnostikovali i adekvatno lečili neposredni i kasni neželjeni efekti antineoplastične terapije.

Komplikacije koje nastaju usled primene konvencionalne hemioterapije (HT), radioterapije (RT), tran-

Oncological treatment often involves simultaneous or successive application of agents with different mechanisms of action in order to potentiate the antineoplastic effect. Targeted therapy with monoclonal antibodies (MABs), as well as with small molecules administered orally, such as tyrosine kinase inhibitors, often involves continuous treatment until disease progression [6]. Tables 1, 2, 3 and 4 list the most important groups of antineoplastic drugs, according to the World Health Organization classification (available at: https://www.whocc.no/atc_ddd_index/), and their mechanisms of action [7–11]. The contemporary approach to the treatment of patients with malignant diseases, in addition to personalized innovative therapy that significantly contributes to its success, but also to the shortening of hospital treatment, also includes careful outpatient monitoring of hemato-oncology patients, in order to prevent, timely diagnose and adequately treat immediate and delayed side effects of antineoplastic treatment.

Table 1. Classes of antineoplastic drugs

Class	Subclass	Drug
Alkylating agents*	Nitrogen mustard analogues	Chlorambucil, Cyclophosphamide, Iphosphamide, bendamustine
	Nitrosoureas	Carmustine, Fotemustine, Semustine, Lomustine, Streptozocin
	Triazens	Dacarbazine
	Ethylene imines and methylamines	Thiotepa
	Alkyl sulfonates	Busulfan
	Epoxides	Etoglucid
	Other alkylating agents	Temozolomide, Dacarbazine, Mitobronitol, Pipobroman
Antimetabolites**	Folic acid analogues	Methotrexate, Pemetrexed, Raltitrexed
	Purine analogues	Azathioprine, Cladribine, Clofarabine, Fludarabine, Mercaptopurine, Nelarabine, Pentostatin, Tioguanine
	Pyrimidine analogues	Doxifluridine, Fluorouracil, Uracil/Tegafur (UFT), Azacytidine, Capecitabine, Cytarabine, Decitabine, Gemcitabine
	Other antimetabolites	Hydroxyurea
Plant alkaloids and other natural products ***	Vinca alkaloids and analogues	Vincristine, Vinblastine, Vindesine, Vinorelbine, Vinflunine, Vintafolide
	Topoisomerase 1 (TOP1) inhibitors	Irinotecan, Topotecan, Belotecan
	Podophyllotoxin derivatives	Etoposide, Teniposide
	Colchicine inhibitors	Demecolcine
	Taxanes	Docetaxel, Paclitaxel, Cabazitaxel
	Other plant alkaloids and natural products	Trabectedin
Cytotoxic antibiotics****	Actinomycines	Dactinomycin
	Anthracyclines	Aclarubicin, Daunorubicin, Doxorubicin, Epirubicin, Mitoxantrone, Pirarubicin
	Other cytotoxic antibiotics	Bleomycin, Mitomycin, Plicamycin

Explanation: Mechanism of action of conventional cytostatic agents –
* Alkylating agents – Modify DNA structure by alkylating nucleic bases (they add methyl groups to guanine and thus prevent DNA transcription and replication), act on all cells in the division phase ('cycle-specific'); ** Antimetabolites – Structural analogues of enzymes involved in DNA synthesis, specific for the S-phase of the cell cycle; *** Plant alkaloids and other natural products – Prevent polymerization of tubulin and synthesis of spindle microtubules or prevent depolymerization of microtubules, stop cell division in the M-phase of the cell cycle; **** Cytotoxic antibiotics – Prevent replication by directly acting on DNA, causing strand separation ('cycle-specific').

Tabela 2. Inhibitori tirozin kinaze

Podklasa	Lek
Inhibitori BCR-ABL tirozin kinaze	Imatinib, Nilotinib, Dasatinib, Bosutinib, Ponatinib, Asciminib
Inhibitori tirozin kinaze EGFR (engl. epidermal growth factor receptor)	Erlotinib, Gefitinib, Ikotinib, Osimertinib
Inhibitori B-Raf serin/treonin kinaze (BRAF)	Vemurafenib, Dabrafenib, Enkorafenib
Inhibitori anaplastične limfomne kinaze (ALK)	Ceritinib, Krizotinib, Alektinib, Brigatinib, Lorlatinib
Inhibitori MEK (engl. mitogen-activated protein kinase)	Trametinib, Kobimetinib, Binimetinib
Inhibitori CDK (engl. cyclin-dependent kinase)	Palbociklib, Ribociklib, Abemaciklib
Inhibitori serin/treonin kinaze mTOR (engl. mammalian target of rapamycin)	Temsirolimus, Everolimus
Inhibitori tirozin kinaze HER2 (engl. human epidermal growth factor receptor 2)	Lapatinib, Neratinib, Tukatinib
Inhibitori tirozin kinaze VEGFR (engl. vascular endothelial growth factor receptor)	Aksitinib, Tivozanib
Inhibitori Brutonove tirozin kinaze (BTK)	Ibrutinib, Akalabrutinib, Zanubrutinib
Inhibitori Fosfatidil-inozitol-3-kinaze (Pi3K)	Idelasilib, Kopanlisib, Alpelisib, Duvelisib
Inhibitori Janus kinaze (JAK)	Ruksolitinib, Fedratinib
Inhibitori FGFR (engl. fibroblast growth factor receptor)	Erdafitinib, Pemigatinib
Inhibitori FLT_3 (engl. FMS-like tyrosine kinase 3)	Midostaurin, Gliteritinib
Multikinazni i ostali inhibitori protein kinaza	Anlotinib, Sorafenib, Midostaurin, Gliteritinib, Lenvatinib, i dr.

Objašnjenje: Mehanizam dejstva konvencionalnih citostatika –
*Alkilirajući agensi – Modifikuju strukturu DNK alkiliranjem nukleinskih baza (dodaju metil grupe na guanin i time onemogućavaju transkripciju i replikaciju DNK), deluju na sve ćelije u fazi deobe („ciklus-specifični"); ** Antimetaboliti – Strukturni analozi enzima koji učestvuju u sintezi DNK, specifični za S-fazu ćelijskog ciklusa; *** Biljni alkaloidi i drugi prirodni produkti – Sprečavaju polimerizaciju tubulina i sintezu mikrotubula deobnog vretena ili sprečavaju depolimerizaciju mikrotubula, zaustavljaju deobu ćelije u M-fazi ćelijskog ciklusa; **** Citotoksični antibiotici – Sprečavaju replikaciju direktnim dejstvom na DNA uzrokujući razdvajanje lanaca („ciklus-specifični").

Table 2. Tyrosine kinase inhibitors

Subclass	Drug
BCR-ABL tyrosine kinase inhibitors	Imatinib, Nilotinib, Dasatinib, Bosutinib, Ponatinib, Asciminib
Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors	Erlotinib, Gefitinib, Icotinib, Osimertinib
B-Raf serine-threonine kinase (BRAF) inhibitors	Vemurafenib, Dabrafenib, Encorafenib
Anaplastic lymphoma kinase (ALK) inhibitors	Ceritinib, Crizotinib, Alectinib, Brigatinib, Lorlatinib
Mitogen-activated protein kinase (MEK) inhibitors	Trametinib, Cobimetinib, Binimetinib
Cyclin-dependent kinase (CDK) inhibitors	Palbociclib, Ribociclib, Abemaciclib
Mammalian target of rapamycin (mTOR) kinase inhibitors	Temsirolimus, Everolimus
Human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors	Lapatinib, Neratinib, Tucatinib
Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors	Axitinib, Tivozanib
Bruton's tyrosine kinase (BTK) inhibitors	Ibrutinib, Akalabrutinib, Zanubrutinib
Phosphatidylinositol-3-kinase (Pi3K) inhibitors	Idelasilib, Copanlisib, Alpelisib, Duvelisib
Janus-associated kinase (JAK) inhibitors	Ruxolitinib, Fedratinib
Fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitors	Erdafitinib, Pemigatinib
FMS-like tyrosine kinase 3 (FLT_3) inhibitors	Midostaurin, Gliteritinib
Multikinase and other protein kinase inhibitors	Anlotinib, Sorafenib, Midostaurin, Gliteritinib, Lenvatinib, etc.

Explanation: Mechanism of action of conventional cytostatic agents –
* Alkylating agents – Modify DNA structure by alkylating nucleic bases (they add methyl groups to guanine and thus prevent DNA transcription and replication), act on all cells in the division phase ('cycle-specific'); ** Antimetabolites – Structural analogues of enzymes involved in DNA synthesis, specific for the S-phase of the cell cycle; *** Plant alkaloids and other natural products – Prevent polymerization of tubulin and synthesis of spindle microtubules or prevent depolymerization of microtubules, stop cell division in the M-phase of the cell cycle; **** Cytotoxic antibiotics – Prevent replication by directly acting on DNA, causing strand separation ('cycle-specific').

Tabela 3. Hormoni, hormonski antagonisti i ostali antineoplastični lekovi

Hormoni i hormonski antagonisti	
Klasa/Podklasa	Lek
Estrogeni	Dietilstilbestrol, Etinilestradiol, Fosfestrol, Poliestradiol fosfat
Progesteroni	Megestrol, Medroksiprogesteron
Inhibitori aromataze	Anastrozol, Letrozol, Eksemestan
Selektivni modulatori estrogenog receptora (SERMs)	Tamoksifen, Raloksifen, Toremifen
Blokatori estrogenskog receptora	Fulvestrant
Agonisti GnRH (engl. gonadotropin-releasing hormone)	Leuprorelin, Goserelin, Triptorelin, Histrelin, Buserelin
Steroidni blokatori androgenskih receptora	Ciproteron-acetat, Dietilsilbestrol
Nesteroidni blokatori androgenskih receptora I generacija II generacija	 Flutamid, Nilutamid, Bikalutamid Abirateron acetat, Enzalutamid
Blokatori sinteze adrenalnih steroida (konverzije holesterola u pregnenolon)	Aminoglutetimid
	Ostali
Kompleksi platine	Karboplatin, Cisplatin, Lobaplatin, Nedaplatin, Oksaliplatin
Inhibitori proteazoma	Bortezomib, Karfilzomib, Iksazomib
Metilhidrazini	Prokarbazin
Retinoidi	Tretinoin (ATRA)
Inhibitori Hedhehog signalnog puta	Glasdegib
Inibitori HDAC (engl. histone deacetylase)	Vorinostat, Romidepsin
Imunomodularni lekovi (IMiD)	Talidomid, Pomalidomid, Lenalidomid
	Arsen trioksid, L-Asparaginaza Irinotekan, Venetoklaks, Anagrelid, Pentostatin, i dr.

Table 3. Hormones, hormone antagonists and other antineoplastic drugs

Hormones and hormone antagonists	
Class/Subclass	Drug
Estrogens	Diethylstilbestrol, Ethinylestradiol, Fosfestrol, Polyestradiol phosphate
Progesterones	Megestrol, Medroxyprogesterone
Aromatase inhibitors	Anastrozole, Letrozole, Exemestane
Selective estrogen receptor modulators (SERMs)	Tamoxifen, Raloxifene, Toremifene
Estrogen receptor blockers	Fulvestrant
Gonadotropin-releasing hormone (GnRH) agonists	Leuprorelin, Goserelin, Triptorelin, Histrelin, Buserelin
Steroid blockers of androgen receptors	Cyproterone acetate, Diethylstilbestrol
Non-steroid blockers of androgen receptors generation I generation II	 Flutamide, Nilutamide, Bicalutamide Abiraterone acetate, Enzalutamide
Adrenal steroid synthesis blockers (blockers of the conversion of cholesterol to pregnenolone)	Aminoglutethimide
Other antineoplastic drugs	
Platinum compounds	Carboplatin, Cisplatin, Lobaplatin, Nedaplatin, Oxaliplatin
Proteasome inhibitors	Bortezomib, Carfilzomib, Ixazomib
Methylhydrazines	Procarbazine
Retinoids for cancer treatment	Tretinoin (ATRA)
Hedgehog pathway inhibitors	Glasdegib
Histone deacetylase (HDAC) inhibitors	Vorinostat, Romidepsin
Immunomodulatory drugs (IMiD)	Thalidomide, Pomalidomide, Lenalidomide
	Arsenic trioxide, L-Asparaginase Irinotecan, Venetoclax, Anagrelide, Pentostatin, etc.

Tabela 4. Monoklonska antitela u hematologiji i onkologiji – ciljni molekuli i terapijsko područje

Antigen	Naziv	Struktura	Terapijska indikacija/godina odobrenja
Nekonjugovana antitela			
PD-L1	Atezolizumab	Humanizovani IgG1	Karcinom mokraćne bešike, nemikrocelularni karcinom pluća (2016), trostruko negativni karcinom dojke (2019)
	Durvalumab	Humani IgG1	Karcinom mokraćne bešike (2017)
	Avelumab	Humani IgG1	Urotelijalni karcinom (2017), karcinom Merkelovih ćelija (2017)
PD-1	Nivolumab	Humani IgG4	Melanom (2014), karcinom pluća (2015), karcinom bubrega (2018)
	Pembrolizumab	Humanizovani IgG4	Melanom (2014), razni maligniteti (2015)
	Cemiplimab	Humani IgG4	Skvamocelularni karcinom kože (2018)
VEGF	Bevacizumab	Humanizovani IgG1	Karcinom kolorektuma (2004), nemikrocelularni karcinom pluća (2006), karcinom bubrega (2009), glioblastom (2009), karcinom ovarijuma (2018)
VEGFR2	Ramucirumab	Humani IgG1	Karcinom želuca (2014)
EGFR	Cetuksimab	Himerični IgG1	Karcinom kolorektuma (2004), skvamocelularni karcinom glave i vrata (2006)
	Necitumumab	Humani IgG1	Nemikrocelularni karcinom pluća (2015)
	Panitumumab	Humani IgG2	Karcinom kolorektuma (2006)
CD38	Daratumumab	Humani IgG1	Multipli mijelom (2015)
	Isatuksimab	Himerični IgG1	Multipli mijelom (2020)
GD2	Dinutuksimab	Himerični IgG1	Neuroblastom (2015)
SLAMF7	Elotuzumab	Humanizovani IgG1	Multipli mijelom (2015)
CTLA-4	Ipilimumab	Humani IgG1	Melanom (2011), karcinom bubrega (2018)
CCR4	Mogamulizumab	Humanizovani IgG1	Kutani T-ćelijski limfom (2018)
PDGFRα	Olaratumab	Humani IgG1	Sarkom (2016)
HER2	Pertuzumab	Humanizovani IgG1	Karcinom dojke (2012)
	Trastuzumab	Humanizovani IgG1	Karcinom dojke (1998)
CD20	Obinutuzumab	Humanizovani IgG2	Hronična limfocitna leukemija (2013)
	Ofatumumab	Humani IgG1	Hronična limfocitna leukemija (2014)
	Rituksimab	Himerični IgG1	B-ćelijski limfomi (1997)
Konjugat antitelo-lek (engl. Antibody–Drug Conjugate (ADC))			
CD33	Gemtuzumab ozogamicin	Humanizovani ADC	Akutna mijeloidna leukemija (2000)
CD30	Brentuksimab vedotin	Himerični ADC	Hočkinov limfom i anaplastični krupnoćelijski limfom (2011)
CD22	Inotuzumab ozogamicin	Humanizovani ADC	Akutna limfoblastna leukemija (2017)
	Moxetumomab pasudotox	Mišji ADC	Hairy-cell leukemija (2018)
CD79B	Polatuzumab vedotin	Humanizovani ADC	B-ćelijski limfomi (2019)
CD20	Ibritumomab tiuxetan	Mišji IgG1-Y90 ili In111	Ne-Hočkinovi limfomi (2002)
	I-131 tositumomab	Mišji IgG2-I131	Ne-Hočkinovi limfomi (2003)
Nectin-4	Enfortumab vedotin	Humani ADC	Karcinom mokraćne bešike (2019)
HER2	Trastuzumab derukstekan	Humanizovani ADC	Karcinom dojke (2019)
	Trastuzumab emtansin	Humanizovani ADC	Karcinom dojke (2013)
TROP2	Sacituzumab govitecan	Humanizovani ADC	Trostruko negativni karcinom dojke (2020)
Bispecifična antitela			
CD19, CD3	Blinatumomab	Akutna limfoblastna leukemija (2014)	
EGFR, MET	Amivantamab	Nemikrocelularni karcinom pluća (2021)	
CD3, IMCgp100	Tebentafusp	Neresektabilan/Metastatski melanom sudovnjače (lat. Melanoma malignum uveae) (2022)	

Legenda: IgG – imunoglobulin G

Table 4. Tyrosine kinase inhibitors

Antigen	Name	Structure	Therapeutic indication/year of approval for use
Unconjugated Antibodies			
PD-L1	Atezolizumab	Humanized IgG1	Urinary bladder carcinoma, non-small cell lung cancer (2016), triple-negative breast cancer (2019)
	Durvalumab	Human IgG1	Urinary bladder carcinoma (2017)
	Avelumab	Human IgG1	Urothelial carcinoma (2017), Merkel cell carcinoma (2017)
PD-1	Nivolumab	Human IgG4	Melanoma (2014), lung carcinoma (2015), renal carcinoma (2018)
	Pembrolizumab	Humanized IgG4	Melanoma (2014), various malignancies (2015)
	Cemiplimab	Human IgG4	Squamous cell carcinoma of the skin (2018)
VEGF	Bevacizumab	Humanized IgG1	Colorectal carcinoma (2004), non-small cell lung cancer (2006), renal carcinoma (2009), glioblastoma (2009), ovarian carcinoma (2018)
VEGFR2	Ramucirumab	Human IgG1	Gastric carcinoma (2014)
EGFR	Cetuximab	Chimeric IgG1	Colorectal carcinoma (2004), Squamous cell carcinoma of the head and neck (2006)
	Necitumumab	Human IgG1	Non-small cell lung cancer (2015)
	Panitumumab	Human IgG2	Colorectal carcinoma ((2006)
CD38	Daratumumab	Human IgG1	Multiple myeloma (2015)
	Isatuximab	Chimeric IgG1	Multiple myeloma (2020)
GD2	Dinutuximab	Chimeric IgG1	Neuroblastoma (2015)
SLAMF7	Elotuzumab	Humanized IgG1	Multiple myeloma (2015)
CTLA-4	Ipilimumab	Human IgG1	Melanoma (2011), renal carcinoma (2018)
CCR4	Mogamulizumab	Humanized IgG1	Cutaneous T-cell lymphoma (2018)
PDGFRα	Olaratumab	Human IgG1	Sarcoma (2016)
HER2	Pertuzumab	Humanized IgG1	Breast carcinoma (2012)
	Trastuzumab	Humanized IgG1	Breast carcinoma (1998)
CD20	Obinutuzumab	Humanized IgG2	Chronic lymphocytic leukemia (2013)
	Ofatumumab	Human IgG1	Chronic lymphocytic leukemia (2014)
	Rituximab	Chimeric IgG1	B-cell lymphomas (1997)
Antibody–Drug Conjugate (ADC)			
CD33	Gemtuzumab ozogamicin	Humanized ADC	Acute myeloid leukemia (2000)
CD30	Brentuximab vedotin	Chimeric ADC	Hodgkin lymphoma and anaplastic large cell lymphoma (2011)
CD22	Inotuzumab ozogamicin	Humanized ADC	Acute lymphoblastic leukemia (2017)
	Moxetumomab pasudotox	Mouse ADC	Hairy-cell leukemia (2018)
CD79B	Polatuzumab vedotin	Humanized ADC	B-cell lymphomas (2019)
CD20	Ibritumomab tiuxetan	Mouse IgG1-Y90 or In111	Non-Hodgkin lymphomas (2002)
	Iodine (I-131) tositumomab	Mouse IgG2-I131	Non-Hodgkin lymphomas (2003)
Nectin-4	Enfortumab vedotin	Human ADC	Urinary bladder carcinoma (2019)
HER2	Trastuzumab deruxtecan	Humanized ADC	Breast carcinoma (2019)
	Trastuzumab emtansine	Humanized ADC	Breast carcinoma (2013)
TROP2	Sacituzumab govitecan	Humanized ADC	Triple-negative breast cancer (2020)
Bispecific antibodies			
CD19, CD3	Blinatumomab	Acute lymphoblastic leukemia (2014)	
EGFR, MET	Amivantamab	Non-small cell lung cancer (2021)	
CD3, IMCgp100	Tebentafusp	Inoperable/Metastatic uveal melanoma (2022)	

Legend: IgG – immunoglobulin G

splantacije matičnih ćelija hematopoeze (TMĆH) i ciljane terapije su kompleksne i multifaktorijalne. One se mogu posmatrati sa nekoliko različitih aspekata:

1. disfunkcija organa i organskih sistema
2. prevremeni smrtni ishod
3. nastanak sekundarnih maligniteta
4. zastoj u rastu i razvoju
5. oštećenje intelektualnih funkcija
6. smanjeni fertilitet
7. smanjeni kvalitet života
8. socijalno-ekonomski aspekt [12].

KARDIOTOKSIČNOST I KARDIO-ONKOLOGIJA

Kardiovaskularne bolesti (KVB) su, uz maligne bolesti, najrasprostranjenije bolesti u razvijenim zemljama, a kardiovaskularni sistem (KVS) je, s obzirom na specifičnost građe i funkcije, posebno osetljiv na antineoplastičnu terapiju. Takođe, pojedini maligniteti, zbog svoje lokalizacije (npr. pluća, medijastinum) i prirodnog toka, utiču na KVS, nezavisno od lečenja. Personalizovani i multidisciplinarni pristup lečenju i praćenju hemato-onkoloških bolesnika je doveo do razvoja nove subspecijalnosti – kardio-onkologije, čiji je osnovni zadatak rano identifikovanje onkoloških bolesnika, sa ili bez pridruženih kardiovaskularnih bolesti, koji imaju povećani rizik od nastanka kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (engl. *cancer therapy-related cardiovascular toxicity – CTR-CVT*), kao i pravovremeno planiranje i sprovođenje dijagnostičko-terapijskih kardioloških procedura koje će se sprovoditi u toku i po završetku onkološkog lečenja, kako bi se poboljšalo preživljavanje i kvalitet života pacijenata [13].

Stoga je brižljiva procena srčane funkcije neophodna prilikom donošenja odluke o vrsti antineoplastične terapije, ali i u toku njene primene, kao i godinama po završetku hemato-onkološkog lečenja. Međunarodno udruženje kardio-onkologa (*International Cardio-Oncology Society – IC-OS*) je definisalo osnovne postulate kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*) [14]. Evropsko udruženje medikalnih onkologa (engl. *European Society for Medical Oncology- ESMO*) je, 2020. godine, dalo prve preporuke za prevenciju, ranu dijagnostiku, praćenje i lečenje kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*) [15], a 2022. godine, objavljene su sveobuhvatne kardio-onkološke smernice nastale konsenzusom eksperata Evropskog udruženja kardiologa (engl. *European Society of Cardiology - ESC*), Evropskog udruženja hematologa (engl. *European Haematology Association - EHA*), Evropskog društva za terapijsku radiologiju i onkologiju (engl. *European Society for Therapeutic Radiology and Oncology - ESTRO*) i *IC-OS*-a [16].

Complications arising from the application of conventional chemotherapy (CT), radiation therapy (RT), hematopoietic stem cell transplantation (HSCT), and targeted therapy are complex and multifactorial. They can be viewed from several different aspects:

1. dysfunction of organs and systems of organs
2. premature death
3. development of secondary malignancies
4. delayed growth and development
5. intellectual impairment
6. reduced fertility
7. reduced quality of life
8. socioeconomic aspect [12].

CARDIOTOXICITY AND CARDIO-ONCOLOGY

Cardiovascular diseases (CVD) are, together with malignant diseases, the most widespread diseases in developed countries, while the cardiovascular system (CVS) is, given the specificity of its structure and function, particularly sensitive to antineoplastic therapy. Also, certain malignancies, due to their localization (e.g., lungs, mediastinum) and their natural progression, affect the CVS, independently of treatment. A personalized and multidisciplinary approach to the treatment and monitoring of hemato-oncology patients has led to the development of a new subspecialty – cardio-oncology, whose main task is the early identification of oncology patients, with or without associated cardiovascular diseases, who have an increased risk of cancer therapy-related cardiovascular toxicity (CTR-CVT), as well as the timely planning and implementation of diagnostic and therapeutic cardiology procedures that will be carried out during and after the completion of oncological treatment, in order to improve patient survival and quality of life [13].

Therefore, a careful assessment of cardiac function is necessary when making a decision on the type of antineoplastic therapy, but also during its application, as well as years after the completion of hemato-oncology treatment. The International Cardio-Oncology Society (IC-OS) defined the basic postulates of CTR-CVT [14]. In 2020, the European Society for Medical Oncology (ESMO) issued the first recommendations for the prevention, early diagnosis, monitoring, and treatment of CTR-CVT [15], and in 2022, comprehensive cardio-oncology guidelines created on the basis of a consensus amongst experts of the European Society of Cardiology (ESC), the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESC), the European Society for Therapeutic Radiology and Oncology - ESTRO) and IC-OS, were published [16].

MEHANIZMI OŠTEĆENJA MIOKARDA ANTINEOPLASTIČNOM TERAPIJOM

Antineoplastična terapija može da dovede do ireverzibilnog oštećenja miokarda (Tip I), ili do disfunkcije kardiomiocita, tj. reverzibilnog oštećenja miokarda (Tip II) [17]. Ireverziblno oštećenje miokarda najčešće izazivaju antraciklini, dok je reverzibilno oštećenje miokarda karakteristika *HER-2* (engl. *human epidermal growth factor receptor 2*) i *VEGFR* (engl. *vascular endothelial growth factor receptor*) inhibitora, kao i inhibitora *BCR-ABL* tirozin kinaze [18].

Osnovni tipovi ćelijske smrti koje nastaju kao posledica kardiotoksičnosti hemato-onkološke terapije (*CTR-CVT*) su autofagija, apoptoza, feroptoza, piroptoza i nekroptoza. Kardiomiociti su veoma bogati mitohondrijama, čija je osnovna funkcija generisanje energije (ATP-adenozin trifosfat) u procesu oksidativne fosforilacije. Najvažniji mehanizam nastanka ireverzibilne kardiotoksičnosti antraciklina je povećano stvaranje kiseoničnih slobodnih radikala (engl. *reactive oxygen species – ROS*) tokom redukcije doksorubicina u doksorubicinol pod dejstvom flavoenzima u prisustvu kiseonika (oksidativni stres), na šta su naročito osetljive mitohondrije, ali i ćelijska membrana, druge organele (endoplazmatični retikulum), kao i jedarna membrana i DNK. Oštećenje membrana mitohondrija dovodi do aktivacije signalnog proteina autofagije *ULK-1* (engl. *unc-51 like autophagy activating kinase 1*), vezivanja mitohondrija za autofagozome i njihovog transporta u lizozome, gde podležu degradaciji. U fiziološkim uslovima, *mTOR* (engl. *mammalian target of rapamycin*) inhibira *ULK-1*. Doksorubicin, osim što oštećuje mitohondrije, inhibira *mTOR* promovišući autofaguju. Oštećenje membrana mitohondrija putem *ROS*-a dovodi do oslobađanja citohroma i aktivacije proapoptotske kaspaze-3, a doksorubicin indukuje apoptozu i aktivacijom tumor- supresorskog gena p53. Apoptoza je znatno potencirana kada se uz doksorubicin istovremeno primenjuju *HER-2* inhibitori. Doksorubicin utiče i na RNK regulatornog proteina feritina i gvožđa (engl. *iron regulatory protein – IRP*) dovodeći do smanjenja koncentracije feritina, a povećanja koncentracije slobodnog gvožđa u ćelijama. U prisustvu slobodnog gvožđa, stvaranje *ROS*-a iz lipidnih peroksida je znatno veće, uzrokujući feroptozu. Aktivacija kaspaze-1 dovodi do oslobađanja proinflamatornih citokina (interleukin (IL)-1 i IL-18) i piroptoze. Aktivacijom *TNF* (engl. *tumor necrosis factor*) signalnog puta, doksorubicin uzrokuje nekroptozu (nekroza posredovana citokinima). Oštećenje endoplazmatičnog retikuluma dovodi do smanjenja vezanog kalcijuma u ćelijama i posledičnog smanjenja kontraktilnosti miocita. Sa druge strane, slobodni Ca^{2+} oštećuje miofibrile aktivacijom proteaza. Takođe, vezivanje doksorubicina

MECHANISMS OF MYOCARDIAL DAMAGE CAUSED BY ANTINEOPLASTIC THERAPY

Antineoplastic therapy can lead to irreversible damage to the myocardium (Type I), or to cardiomyocyte dysfunction, i.e., reversible myocardial damage (Type II) [17]. Irreversible myocardial damage is most often caused by anthracyclines, while reversible myocardial damage is a characteristic of HER-2 (human epidermal growth factor receptor 2) and VEGFR (vascular endothelial growth factor receptor) inhibitors, as well as of BCR-ABL tyrosine kinase inhibitors [18].

The main types of cell death that occur as the result of CTR-CVT are autophagy, apoptosis, ferroptosis, pyroptosis and necroptosis. Cardiomyocytes are very rich in mitochondria, whose main function is to generate energy (ATP-adenosine triphosphate) in the process of oxidative phosphorylation. The most important mechanism of irreversible cardiotoxicity of anthracyclines is the increased generation of oxygen free radicals (reactive oxygen species - ROS) during the reduction of doxorubicin to doxorubicinol under the influence of flavoenzymes in the presence of oxygen (oxidative stress), to which mitochondria are especially sensitive, as is the cell membrane, other organelles (endoplasmic reticulum), as well as the nuclear membrane and DNA. Damage to mitochondrial membranes leads to the activation of the autophagy signaling protein ULK-1 (unc-51 like autophagy activating kinase 1), and to the binding of mitochondria to autophagosomes and their transport to lysosomes, where they undergo degradation. Under physiological conditions, mTOR (mammalian target of rapamycin) inhibits ULK-1. Doxorubicin, in addition to damaging mitochondria, inhibits mTOR by promoting autophagy. Damage to mitochondrial membranes through ROS leads to the release of cytochromes and activation of proapoptotic caspase-3, while doxorubicin induces apoptosis by activating the tumor suppressor gene p53. Apoptosis is significantly potentiated when HER-2 inhibitors are administered simultaneously with doxorubicin. Doxorubicin also affects the RNA of the regulatory protein ferritin and iron (iron regulatory protein - IRP), leading to a decrease in the concentration of ferritin and an increase in the concentration of free iron in cells. In the presence of free iron, the generation of ROS from lipid peroxides is significantly higher, causing ferroptosis. Caspase-1 activation leads to the release of pro-inflammatory cytokines (interleukin (IL)-1 and IL-18) and pyroptosis. By activating the TNF (tumor necrosis factor) signaling pathway, doxorubicin causes necroptosis (cytokine-mediated necrosis). Damage to the endoplasmic reticulum leads to a decrease in protein-bound calcium in cells and a consequent decrease in myocyte contractility. On the

za sintetazu azot monoksida (NO) u endotelu uzrokuje smanjenu sintezu azot monoksida, veoma važne endogene vazoaktivne supstancije. Ovi procesi nisu karakteristični samo za miokard, ali, za razliku od drugih tkiva, miokard sadrži veoma malo katalaza koje inaktivišu slobodne radikale [5,18]. Detektovano je 40 gena čiji polimorfizam doprinosi nastanku antraciklinske kardiotoksičnosti, ali se genetsko ispitivanje još uvek ne preporučuje [19].

Ireverzibilno oštećenje miokarda je dozno-zavisno [20]. Preporučene maksimalne kumulativne doze pojedinih konvencionalnih citostatika kod odraslih pacijenata su: doksorubicin – 550 mg/m^2 (ukoliko se primenjuje u hemoterapijskim ciklusima na 21 dan), uz kardiološko praćenje pri kumulativnim dozama većim od 300 mg/m^2; daunorubicin – od 400 do 550 mg/m^2; epirubicin – 900 mg/m^2; idarubicin – 150 mg/m^2; mitoksantron – 140 mg/m^2; dok ciklofosfamid u pojedinačnoj dozi >150 mg/kg (ili 1,55 g/m^2/d), koja se primenjuje prilikom TMĆH-a, može dovesti do iznenadne srčane smrti [18].

KLINIČKE MANIFESTACIJE KARDIOTOKSIČNOSTI UZROKOVANE HEMATO-ONKOLOŠKOM TERAPIJOM (*CTR-CVT*)

Prema vremenu nastanka, kardiotoksičnost uzrokovana hemato-onkološkom terapijom (*CTR-CVT*) može biti: rana, koja nastaje u toku samog hemato-onkološkog lečenja, i kasna, koja se ispoljava i godinama po završetku lečenja malignih bolesti. Klinički, oštećenje KVS-a se manifestuje nastankom:

1) srčane insuficijencije (SI)/kardijalne disfunkcije
2) arterijske hipertenzije
3) produžetka *QT* intervala i aritmija (supraventrikularne aritmije, ventrikularne aritmije, bradikardija, atrijalna fibrilacija/flater)
4) miokarditisa/perikarditisa
5) vaskularnih poremećaja (arterijske i venske tromboze) [14-17].

U Tabeli 5 su navedeni lekovi koji najčešće dovode do određenih kliničkih manifestacija kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*).

Na povećani rizik od nastanka kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*) naročito ukazuju sledeće karakteristike bolesnika:

1. prethodna antineoplastična terapija (primena antraciklina, konkomitantna ili sukcesivna primena antraciklina i *HER-2* inhibitora, prethodna RT grudnog koša i medijastinuma)
2. životno doba (stariji od 75 godina i mlađi od 10 godina)

other hand, free Ca^{2+} damages myofibrils by activating proteases. Also, the binding of doxorubicin to nitrogen monoxide (NO) synthetase in the endothelium causes reduced synthesis of nitrogen monoxide, a very important endogenous vasoactive substance. These processes are not only characteristic of the myocardium, but, unlike other tissues, the myocardium contains very few catalases that inactivate free radicals [5,18]. Forty genes, whose polymorphism contributes to anthracycline cardiotoxicity, have been detected, but genetic testing is still not recommended [19].

Irreversible myocardial damage is dose-dependent [20]. The recommended maximum cumulative doses of some conventional cytostatic agents in adult patients are, as follows: doxorubicin – 550 mg/m^2 (if applied in chemotherapy cycles every 21 days), with cardiological monitoring at cumulative doses higher than 300 mg/m^2; daunorubicin – between 400 and 550 mg/m^2; epirubicin – 900 mg/m^2; idarubicin – 150 mg/m^2; mitoxantrone – 140 mg/m^2; while cyclophosphamide in a single dose >150 mg/kg (or 1.55 g/m^2/d), administered during HSCT, can lead to sudden cardiac death [18].

CLINICAL MANIFESTATIONS OF CTR-CVT

According to the time of occurrence, CTR-CVT can be early, which occurs during the hemato-oncology treatment itself, and late, which manifests years after the end of the treatment of malignant diseases. Clinically, CVS damage is manifested by the appearance of the following:

1) heart failure (HF)/cardiac dysfunction
2) arterial hypertension
3) prolonged QT interval and arrhythmias (supraventricular arrhythmias, ventricular arrhythmias, bradycardia, atrial fibrillation/flutter)
4) myocarditis/pericarditis
5) vascular disorders (arterial and venous thrombosis) [14-17].

Table 5 lists the drugs that most commonly lead to certain clinical manifestations of CTR-CVT.

The following patient characteristics particularly indicate an increased risk of CTR-CVT:

1. previous antineoplastic therapy (administration of anthracyclines, concomitant or successive administration of anthracyclines and HER-2 inhibitors, previous RT of the chest and mediastinum)
2. age (persons above the age of 75 and below the age of 10)
3. smoking status (active and former smokers) and obesity (BMI > 30 kg/m^2)
4. comorbidities: diabetes (HbA1c > 7.0% or > 53 mmol/mol), chronic kidney failure (eGFR

Tabela 5. Kliničke manifestacije kardiotoksičnosti i antineoplastični lekovi koji ih najčešće uzrokuju

Kliničke manifestacije	Antineoplastični agensi
Disfunkcija miokarda/Srčana slabost	Antraciklini, *HER2At*, inhibitori *VEGF* tirozin kinaze, *mVEGFAt*, inhibitori *BCR-ABL* tirozin kinaze
Akutni koronarni sindrom	
• Promocija ateroskleroze i ruptura plaka	GnRH agonisti, inhibitori *PD-1* i *PD-L1*, Nilotinib, Ponatinib, *VEGFi*, RT
• Vazospazam	Bleomicin, analozi pirimidina, taksani, *VEGF* inhibitori, vinka alkaloidi
• Tromboza koronarnih arterija	Alkilirajući agensi, Erlotinib, inhibitori *PD-1* i *PD-L1*, *IMiD* (Lenalidomid, Talidomid), mAt (*VEGFi*, *anti-CD20*), Nilotinib, kompleksi platine, inhibitori proteazoma, Ponatinib
Hronični koronarni sindrom	Fluorouracil, Kapecitabin, kompleksi platine, inhibitori *VEGF* tirozin kinaze, *mVEGFAt*
Produžetak QT intervala	Arsen trioksid, Glasdegib Nilotinib, Oksaliplatin, Pazopanib, Ribociklib, Sunitinib, Toremifen, Vandetanib
Miokarditis/Perikarditis	*inhibitori PD-1* i *PD-L1*

Legenda: m – monoklonska; At – antitelo; *HER2 – human epidermal growth factor receptor 2; VEGFi – vascular endothelial growth factor; GnRH – gonadotropin-releasing hormone; PD1 – programmed cell death protein; PD-L1 – programmed death-ligand;* RT – radioterapija; *IMiD* – imunomodulatorni lekovi *(engl. immunomodulatory drugs)*

Table 5. Clinical manifestations of cardiotoxicity and the antineoplastic drugs that are most commonly their cause

Clinical manifestation	Antineoplastic agents
Myocardial disfunction/Heart failure	Anthracyclines, mHER2Ab, VEGF tyrosine kinase inhibitors, mVEGFAb, BCR-ABL tyrosine kinase inhibitors
Acute coronary syndrome	
• Accelerated atherosclerosis and plaque rupture	GnRH agonists, PD-1 and PDL1 inhibitors, Nilotinib, Ponatinib, VEGFi, RT,
• Vasospasm	Bleomycin, pyrimidine analogues, taxanes, VEGF inhibitors, vinca alkaloids
• Coronary thrombosis	Alkylating agents, Erlotinib, PD-1 and PDL1 inhibitors, IMiD (lenalidomide, thalidomide), mAb (VEGFi, anti-CD20), Nilotinib, platinum compounds, proteasome inhibitors, Ponatinib,
Chronic coronary syndrome	Fluorouracil, Capecitabine, platinum compounds, VEGF tyrosine kinase inhibitors, mVEGFAb
QT prolongation	Arsenic trioxide, Glasdegib Nilotinib, Oxaliplatin, Pazopanib, Ribociclib, Sunitinib, Toremifene, Vandetanib
Myocarditis/Pericardtis	PD-1 and PDL1 inhibitors

Legend: m – monoclonal; Ab – antibody; HER2 – human epidermal growth factor receptor 2; VEGFi – vascular endothelial growth factor; GnRH – gonadotropin-releasing hormone; PD1 – programmed cell death protein; PD-L1 – programmed death-ligand; RT – radiation therapy; IMiD – immunomodulatory drugs

3. pušački status (aktivni i bivši pušači) i gojaznost (*BMI* > 30 kg/m^2)
4. komorbiditeti: šećerna bolest (HbA1c > 7,0% ili > 53 mmol/mol), hronična bubrežna slabost (eGFR < 60 ml/min/1,73 m^2), dislipidemija (ne HDL holesterol > 3,5 mmol/l)
5. kardiovaskularni status: arterijska hipertenzija (sistolni pritisak > 140 mmHg, dijastolni pritisak > 90 mmHg), povišeni kardiospecifični enzimi pre započinjanja lečenja, ejekciona frakcija leve komore (EFLK) < 50%.

< 60 ml/min/1.73 m^2), dyslipidemia (non-HDL cholesterol > 3.5 mmol/l)

5. cardiovascular status: arterial hypertension (systolic pressure > 140 mmHg, diastolic pressure > 90 mmHg), elevated level of cardiospecific enzymes before starting treatment, left ventricular ejection fraction (LVEF) < 50%.

Based on the above-described factors, all patients are classified into the following three groups: patients with low risk, patients with medium risk, and those with moderately high or high risk of developing CTR-CVT [15,16].

Na osnovu navedenih faktora, svi bolesnici se svrstavaju u tri rizične grupe: bolesnici sa niskim, srednjim i umereno visokim/visokim rizikom od razvoja kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*) [15,16].

DIJAGNOSTIČKE PROCEDURE U PRIMARNOJ I SEKUNDARNOJ PREVENCIJI KARDIOTOKSIČNOSTI UZROKOVANE HEMATO-ONKOLOŠKOM TERAPIJOM *(CTR-CVT)*

Pre primene antineoplastične terapije, neophodno je da se svim bolesnicima uradi elektrokardiogram (EKG). Produžetak *QT* intervala (> 500 ms) predstavlja prvi znak poremećaja repolarizacije miokarda i mogućnosti nastanka fatalnih aritmija, naročito ukoliko su udružene sa elektrolitnim disbalansom (niske koncentracije kalijuma, magnezijuma i kalcijuma) ili konkomitantnom primenom nekih antibiotika i antiemetika.

Transtorakalna 3D ehokardiografija (TTE) je takođe ustanovljena standardna procedura koja se sprovodi pre započinjanja svakog onkološkog lečenja i prilikom koje se procenjuje funkcija leve komore (LK), desne komore (DK), dilatacija srčanih šupljina, hipertrofija leve komore, regionalni poremećaji kontraktilnosti, dijastolna funkcija, valvularne mane, pritisak u plućnim arterijama i stanje perikarda. Bezbednom se smatra EFLK > 50%. Bolesnike sa povećanim rizikom neophodno je ehokardiografski redovno pratiti. Svaki pad EFLK ≥ 10% ili pad procenta longitudinalnog skraćenja leve komore (engl. *global longitudinal strain – GLS*) > 15% ukazuje na disfunkciju miokarda [21]. U slučajevima kada se TTE nalaz ne može adekvatno interpretirati, indikovana je kardiomagnetna rezonanca [16].

Kod onkoloških bolesnika sa kardiovaskularnim oboljenjem neophodno je odrediti srčane markere: visokosenzitivni troponin I (engl. *high-sensitivity troponin I – hs troponin I*) kao i natriuretske peptide (NP) – B-tip NP (BNP) i N-terminalni pro-BNP (NT-proBNP), pre započinjanja lečenja, i redovno ih pratiti tokom hemato-onkološke terapije, naročito u toku primene antraciklina. Rani porast *hs* troponina I > 99-og percentila, BNP ≥ 35 pg/ml i pro-BNP ≥ 125 pg/ml, u toku primene antineoplastične terapije, ukazuje na razvoj kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*) [14 –16].

LEKOVI KOJI SE PRIMENJUJU ZA PRIMARNU I SEKUNDARNU PREVENCIJU KARDIOTOKSIČNOSTI UZROKOVANE HEMATO-ONKOLOŠKOM TERAPIJOM *(CTR-CVT)*

Deksrazoksan i lipozomalni obilici konvencionalnih citostatika su jedini lekovi odobreni za prevenciju kar-

DIAGNOSTIC PROCEDURES IN PRIMARY AND SECONDARY PREVENTION OF CTR-CVT

Before administering antineoplastic therapy, it is necessary for all patients to have an electrocardiogram (ECG). Prolongation of the QT interval (> 500 ms) is the first sign of myocardial repolarization disorders and of the possibility of fatal arrhythmias, especially if they are associated with electrolyte imbalance (low concentrations of potassium, magnesium and calcium) or with the concomitant use of certain antibiotics and antiemetics.

Transthoracic 3D echocardiography (TTE) is also a standard procedure that is performed before starting any oncological treatment and during which the left ventricular (LV) function, right ventricular (RV) function, dilatation of cardiac chambers, left ventricular hypertrophy, regional contractility disorders, diastolic function, valvular defects, pulmonary artery pressure, and the condition of the pericardium, are evaluated. LVEF > 50% is considered safe. Patients with increased risk must be monitored regularly with echocardiography. Any decrease in LVEF ≥ 10% or decrease in global longitudinal strain (GLS) > 15% indicates myocardial dysfunction [21]. In cases where TTE findings cannot be adequately interpreted, cardiac magnetic resonance imaging should be performed [16].

In oncology patients with cardiovascular disease, it is necessary to determine the cardiac markers: high-sensitivity troponin I (hs troponin I) as well as natriuretic peptides (NP) – B-type NP (BNP) and N-terminal pro-BNP (NT-proBNP), before starting treatment, and to monitor them regularly during hemato-oncology treatment, especially during the administration of anthracyclines. Early increase in hs troponin I > 99th percentile, BNP ≥ 35 pg/ml, and pro-BNP ≥ 125 pg/ml, during the use of antineoplastic therapy, indicates the development of CTR-CVT [14 – 16].

DRUGS USED FOR PRIMARY AND SECONDARY PREVENTION OF CTR-CVT

Dexrazoxane and liposomal forms of conventional cytostatic agents are the only drugs approved for the prevention of CTR-CVT, primarily heart failure caused by anthracyclines. Dexrazoxane, an iron chelator and topoisomerase I inhibitor, is officially approved for use in breast cancer patients who are at high risk of CTR-CVT and who have previously received a cumulative dose of doxorubicin of at least 300 mg/m^2 (or anthracycline equivalent). Intravenous infusion of dexrazoxane is administered 30 minutes before each cycle of chemotherapy protocol containing anthracyclines, in a dose of 10:1 (e.g., 500 mg dexrazoxane : 50 mg

diotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*), pre svega srčane insuficijencije uzrokovane antraciklinima. Deksrazoksan, helator gvožđa, inhibitor topoizomeraze I, zvanično je odobren za primenu kod bolesnica sa karcinomom dojke koje su pod velikim rizikom od nastanka kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*), a koje su prethodno već primile kumulativnu dozu doksorubicina od najmanje 300 mg/m^2 (ili antraciklinski ekvivalent). Intravenska infuzija deksrazoksana se primenjuje 30 minuta pre svakog ciklusa hemioterapijskog protokola koji sadrži antracikline, u dozi 10:1 (npr. 500 mg deksrazoksana : 50 mg doksorubicina) [22]. Međutim, njegova primena može biti povezana sa smanjenim odgovorom na antineoplastičnu terapiju kao i sa povećanom incidencijom sekundarnih maligniteta [18].

Kod bolesnika sa visokom *CVR-CVT* se primenjuju i lipozomalni oblici konvencionalnih citostatika – pegilovani ili nepegilovani lipozomalni daunorubicin, ili fiksna kombinacija lipozomalnog daunorubicina i citarabina, koji je odobren za lečenje akutne mijeloidne leukemije [23].

Za primarnu prevenciju kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*) kod visokorizičnih bolesnika, preporučuje se primena *ACE-I* (engl. *angiotensin-converting enzyme*) inhibitora, *ARB*-a (engl. *angiotensin receptor blockers*), kao i statina [16]. Dokazano je da bolesnici sa malignim bolestima, naročito u uznapredovalim stadijumima i agresivnijih histoloških tipova, imaju poremećaj lipidnog profila [24, 25], a statini, pored kardioprotektivnog dejstva, imaju i antineoplastični efekat, uzrokujući apoptozu malignih ćelija [26, 27].

Veoma je važno istaći da mnogi konvencionalni i savremeni antineoplastični lekovi imaju izražene interakcije sa drugim lekovima (npr. antiepileptici, antipsihotici, lekovi koji je metabolišu putem citohroma, lekovi koji utiču na pH želuca), kao i sa hranom (npr. sok od grejpfruta) što može uzrokovati poremećaj u resorpciji, metabolizmu i ekskreciji antineoplastičnog leka, a samim tim i njegove smanjene/povećane koncentracije u organizmu, što utiče ne samo na antineoplastični efekat već i nosi rizik od toksičnih efekata, uključujući i *CTR-CVT*. Stoga je neophodno detaljno upoznati bolesnika o svim mogućim neželjenim efektima konkomitantne terapije i neophodnosti striktnog poštovanja vremenskog sleda uzimanja lekova [16].

U sekundarnoj prevenciji, tj. kod bolesnika koji imaju pridruženu KVB ili *CTR-CVT*, ispoljenu u toku ranijeg ili trenutnog hemato-onkološkog lečenja, neophodno je redovno kliničko praćenje, uključujući i kontrole srčanih biomarkera, 12-kanalnog EKG-a i TTE-a, uz adekvatnu terapiju. Definisani su protokoli

doxorubicin) [22]. However, its use may be associated with a reduced response to antineoplastic therapy as well as an increased incidence of secondary malignancies [18].

In patients with high CVR-CVT, liposomal forms of conventional cytostatic agents are also administered – pegylated or non-pegylated liposomal daunorubicin, or a fixed combination of liposomal daunorubicin and cytarabine, which has been approved for the treatment of acute myeloid leukemia [23].

For primary prevention of CTR-CVT in high-risk patients, the use of angiotensin-converting enzyme (ACE-I) inhibitors, angiotensin receptor blockers (ARBs), as well as statins, is recommended [16]. It has been proven that patients with malignant diseases, especially in advanced stages and with more aggressive histological types, have a lipid profile disorder [24, 25], and statins, in addition to their cardioprotective effect, also have an antineoplastic effect, causing apoptosis of malignant cells [26, 27].

It is very important to emphasize that many conventional and novel antineoplastic drugs have pronounced interactions with other drugs (e.g., antiepileptics, antipsychotics, drugs metabolized by cytochromes, drugs that affect gastric pH), as well as with food (e.g., grapefruit juice), which can cause a disruption in the resorption, metabolism, and excretion of the antineoplastic drug, and therefore its reduced/increased concentration in the body, which affects not only the drug's antineoplastic effect but also carries the risk of toxic effects, including CTR-CVT. Therefore, it is necessary to inform the patient, in detail, about all possible side effects of concomitant therapy and the necessity of strictly observing the time sequence of drug intake [16].

In secondary prevention, i.e., in patients who have an associated CVD or CTR-CVT, which manifested during previous or current hemato-oncology treatment, regular clinical follow-up is necessary, including the follow-up of cardiac biomarkers, 12-channel ECG, and TTE, together with appropriate therapy. Follow-up and therapeutic approach protocols in secondary prevention of CTR-CVT have been defined for the most commonly used groups of antineoplastic agents, for the most common drug combinations used in the treatment of certain malignant diseases (multiple myeloma, prostate cancer, breast cancer), for radiotherapy (RT), as well as for hematopoietic stem cell transplantation (HSCT). Depending on the severity of manifested CTR-CVT, antineoplastic therapy can be continued or temporarily or permanently discontinued [15,16].

Drugs used for secondary prevention depend on the clinical manifestation of CTR-CVT.

praćenja i terapijskog pristupa u sekundarnoj prevenciji kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*) za najčešće primenjivane grupe antineoplastičnih agenasa, za najčešće kombinacije lekova koji se primenjuju u lečenju određenih malignih bolesti (multipli mijelom, karcinom prostate, karcinom dojke), za radioterapiju (RT), kao i za transplantaciju matičnih ćelija hematopoeze (TMĆH). U zavisnosti od težine ispoljene kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*), antineoplastična terapija se može nastaviti, te privremeno ili trajno obustaviti [15,16].

Lekovi koji se primenjuju u sekundarnoj prevenciji zavise od kliničke manifestacije kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*).

- Za lečenje novonastale srčane disfunkcije/SI se primenjuju *ACE-I*, *ARB* i/ili beta blokatori, uz inicijalne redovne kontrole TTE-a na 2 – 3 nedelje u toku antineoplastične terapije (ukoliko njen nastavak nije kontraindikovan), kao i 6 i 12 meseci po završetku hemato-onkološkog lečenja.
- Za lečenje miokarditisa, čiji su najčešći uzrok u poslednjih nekoliko godina inhibitori kontrolne tačke (engl. *immune checkpoint inhibitors*) klase *PD-1* (engl. *programmed cell death protein 1*) i klase *PD-L1* (engl. *programmed death-ligand*), preporučuju se kortikosteroidi. Inicijalna terapija za fulminantne forme, koje zahtevaju bolničko lečenje, jeste metilprednizolon u dozi 500 – 1.000 mg/d i.v., tokom tri dana, potom prednizon 1 mg/kg sa taperingom od 10 mg/nedeljno do doze od 20 mg/dan, i nakon toga laganim smanjenjem doze za 5 mg/nedeljno, uz redovno praćenje troponina. Kod kortikorezistentnih bolesnika, u drugoj terapijskoj liniji se mogu primeniti mikofenolat-mofetil, antitimocitni imunoglobulin, tocilizumab, abatacept, alemtuzumab, terapijska izmena plazme, kao i inhibitori Janus kinaze 2 (JAK-2) [28].
- Lečenje akutnog koronarnog sindroma koji nastane u toku aktivnog hemato-onkološkog lečenja je veoma kompleksno. Maligne bolesti predstavljaju hronično proinflamatorno i protrombogeno stanje, a očekivane hematološke komplikacije koje prate antineoplastičnu terapiju (anemija, trombocitopenija, febrilna neutropenija) ograničavaju mogućnost optimalnog lečenja, naročito mogućnost primene antiagregacione terapije i hirurških procedura [16]. U slučaju trombocitopenije od < $20x10^9$/l, savetuje se da se pre kateterizacije daju transfuzije trombocita (Tr), te da se primeni radijalni pristup uz brižljivu hemostazu i male doze heparina (30 – 50 U/kg). Aspirin se obustavlja pri broju Tr <$10x10^9$/l, klopidogrel pri Tr < $30x10^9$/l, a prasugrel i tikagre-

- For the treatment of new-onset cardiac dysfunction/HF, ACE-I, ARB and/or beta blockers are used, with initial regular TTE check-ups every 2 – 3 weeks during antineoplastic therapy (if its continuation is not contraindicated), as well as 6 and 12 months after the completion of hemato-oncology treatment.
- For the treatment of myocarditis, which, in recent years, has been most commonly caused by immune checkpoint inhibitors of programmed cell death protein 1 (PD-1) and programmed death-ligand (PD-L1), corticosteroids are recommended. Initial therapy for fulminant forms, which require hospital treatment, is methylprednisolone at a dose of 500 – 1,000 mg/d IV, for three days, then prednisone 1 mg/kg, with a tapering of 10 mg/week to a dose of 20 mg/day, and after that slow reduction of the dose by 5 mg/week, with regular monitoring of troponin. In corticosteroid-resistant patients, mycophenolate mofetil, antithymocyte immunoglobulin, tocilizumab, abatacept, alemtuzumab, therapeutic plasma exchange, and Janus kinase 2 (JAK-2) inhibitors, can be used as second-line treatment [28].
- The treatment of acute coronary syndrome which develops during active hemato-oncology treatment is very complex. Malignant diseases represent a chronic proinflammatory and prothrombogenic state, and the expected hematological complications accompanying antineoplastic therapy (anemia, thrombocytopenia, febrile neutropenia) limit the possibility of optimal treatment, especially the possibility of applying antiplatelet therapy and surgical procedures [16]. In case of thrombocytopenia of < $20x10^9$/l, it is advised to administer platelet (PLT) transfusions before catheterization, and to apply the radial approach with careful hemostasis and low doses of heparin (30 – 50 U/kg). Aspirin is discontinued when the platelet count is PLT < $10x10^9$/l, clopidogrel is discontinued at PLT < $30x10^9$/l, and prasugrel and ticagrelor are discontinued at PLT < $30x10^9$/l. The recommended minimum platelet count for percutaneous coronary intervention (PCI) is $30x10^9$/l, and for coronary artery bypass grafting (CABG) $50x10^9$/l [29].
- Venous thromboembolism (deep vein thrombosis and pulmonary embolism) is treated with anticoagulation therapy, in keeping with the protocols, with dose modification depending on the number of platelets. Individual thrombogenic risk can be assessed using clinical scores (Khorana, Padua, Caprini), taking into account comorbidities, laboratory parameters, as well as the type of malignancy.

lol ukoliko je broj Tr < $30x10^9$/l. Preporučeni minimalni broj Tr za perkutanu koronarnu intervenciju (engl. *percutaneous coronary intervention – PCI*) iznosi $30x10^9$/l, a za koronarni arterijski bajpas grafting (engl. *coronary artery bypass grafting – CABG*) $50x10^9$/l [29].

- Venski tromboembolizam (tromboze dubokih vena i plućna embolija) se leči antikoagulantnom terapijom, prema protokolima, uz korekciju doze u zavisnosti od broja trombocita. Individualni trombogeni rizik se može proceniti pomoću kliničkih skorova (*Khorana, Padua, Caprini*), uzimajući u obzir komorbiditete, laboratorijske parametre, kao i tip maligniteta. Neoplazme sa najvećim protrombogenim rizikom su karcinom želuca i pankreasa, dok karcinom pluća, bubrega, testisa, mokraćne bešike, ginekološki maligniteti, kao i limfomi nose visok rizik od razvoja venskih tromboza.. U toku aktivnog onkološkog lečenja, preporučuje se primena niskomolekularnog heparina. Primena direktnih oralnih antikoagulanasa (DOAK), apiksabana, rivaroskabana i edoksabana, može povećati rizik od krvarenja budući da su ovo potentni inhibitori citohroma P450 (podtip *CYP3A4*) i/ili P-glikoproteina (P-gp) i potreban je veliki oprez prilikom konkomitantne primene ovih lekova sa konvencionalnim citostaticima (antraciklini, alkilirajući agensi), monoklonskim antitelima i malim molekulima. Antineoplastični lekovi utiču i na koncentraciju varfarina koji se metaboliše preko *CYP2C9* i mogu dovesti ili do povećanog rizika od krvarenja (antagonisti pirimidina, neki antraciklini, obinutuzumab, pegilovani interferon alfa 2a, inhibitori Brutonove kinaze, inhibitori BCR/ABL kinaze) ili pak indukcijom *CYP2C9* dovesti do smanjene koncentracije varfarina i povećati rizik od tromboze (analozi purina, biljni alkaloidi, estrogeni, inhibitori anaplastične limfomne kinaze (ALK)) [16,30].

ZAKLJUČAK

Maligne bolesti i KVB su načešći uzrok morbiditeta i mortaliteta savremenog društva. Prevencija, pravovremena dijagnostika i adekvatno zbrinjavanje kardiotoksičnosti uzrokovane hemato-onkološkom terapijom (*CTR-CVT*), nastale primenom konvencionalne i savremene antineoplastične terapije, zahtevaju multidisciplinarni pristup, što je dovelo do razvoja kardio-onkologije i zajedničkih hemato-onkološko-kardioloških smernica, u cilju dužeg preživljavanja i boljeg kvaliteta života obolelih.

Sukob interesa: Nije prijavljen.

Neoplasms with the highest prothrombogenic risk are stomach and pancreatic cancer, while lung, kidney, testicular, and urinary bladder cancer, gynecological malignancies, as well as lymphomas, carry a high risk of venous thrombosis. During active oncological treatment, the use of low-molecular-weight heparin is recommended. The use of direct oral anticoagulants (DOACs), apixaban, rivaroxaban and edoxaban, may increase the risk of bleeding as these are potent inhibitors of cytochrome P450 (CYP3A4 subtype) and/or P-glycoprotein (P-gp), and particular caution is required when these drugs are concomitantly administered with conventional cytostatic agents (anthracyclines, alkylating agents), monoclonal antibodies and small molecules. Antineoplastic drugs also affect the concentration of warfarin, which is metabolized via CYP2C9 and can either lead to an increased risk of bleeding (pyrimidine antagonists, some anthracyclines, obinutuzumab, pegylated interferon alfa 2a, Bruton's kinase inhibitors, BCR/ABL kinase inhibitors) or, by the induction of CYP2C9, they can lead to reduced warfarin concentration and increase the risk of thrombosis (purine analogues, plant alkaloids, estrogens, anaplastic lymphoma kinase (ALK) inhibitors) [16,30].

CONCLUSION

Malignant diseases and CVDs are the most common causes of morbidity and mortality in modern society. Prevention, timely diagnosis and appropriate treatment of CTR-CVT, caused by the application of conventional and modern antineoplastic therapy, require a multidisciplinary approach. This is what has led to the development of cardio-oncology, as well as to the development of common hemato-oncology-cardiology guidelines, with the aim of achieving longer survival and a better quality of life for patients.

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