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Recent findings of cardiac dysfunction and anti-cancer therapy

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Abstract

Cardiovascular diseases and carcer have a lot of things in common. Both of those conditions are responsible for most deaths in first world countries. Moreover, considerable amount of heart dysfunction complications, result from cancer treatment. For example, common anticancer drugs like anthracyclines are cardiotoxic. Administrations of these compounds may cause cardiotoxicity type I. Trastuzumab is also a compound that is used in cancer treatment, sometimes used concurrently with anthracyclines, and this drug is associated with cardiotoxicity type II. These drugs and many others have side effects ranging from mild to severe like irreversible cardiac damage that may result in heart failure. Cyclophosphamide is a chemotherapy medication used to treat various types of cancer and also can be useful to treat autoimmunological conditions. Radiotherapy, also known as radiation therapy, is a medical treatment that uses high doses of radiation to kill cancer cells and shrink tumors. It is also a stressful treatment on the cardiovascular system to such degree, that the second most fatal complication after utilizing radiotherapy is heart dysfunction. Pre-existing cardiovascular disease can influence the treatment as well as the prognosis of the patient. Patients with former cardiovascular disease are associated with less treatment options, significantly higher likelihood of worse treatment outcomes and complications that often result in death.

Running title: Cardiac dysfunction and anti-cancer therapy

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Introduction

Cardiovascular diseases and cancers are classified as the most common causes of death in developed countries, while in developing ones, prospective analysis indicates their presence at the top of the hierarchy by 2030 [1]. The risk of developing cardiovascular disease surpasses the risk of cancer recurrence in oncology patients who have survived, which can be linked to the impact of cancer therapy [2]. According to recent reports, 8.8% of long-term cancer survivors die prematurely due to coexisting cardiovascular diseases. Simultaneously, the presence of these conditions in cancer patients contributes to a 3.78-fold higher mortality rate from any cause compared to patients not suffering from cardiovascular anomalies [3]. The significance of the problem can be traced through the example of the hospital in Ottawa, where in 2008 a department dedicated to improving the monitoring of oncology patients at risk of cardiovascular exposure was established. Initially, the largest percentage of admissions were breast cancer patients, but the development associated with the emergence of new cancer treatment strategies with a high degree of cardiotoxicity has diversified the reasons for patient acquisition [4].

In view of the above, due to the increasing prevalence of cancer therapies, their significant, destructive impact on the cardiovascular system, and the resulting global concern, a relatively new domain of medical sciences called cardio-oncology was formed in the 1990s [5,6]. One of the tasks of individuals working in this field is to unmask the toxicity of cancer therapy and initiate possible interventions without disrupting the treatment of the primary disease [7]. This toxicity can manifest in short-term or long-term consequences and may contribute to the intensification or concealment of already existing heart diseases [8]. Due to the increase in cancer patient survival rates, there is currently talk of disease entities developed among survivors, such as cancer therapeutics-related cardiac dysfunction (CTRCD) or linked to it – radiation-induced heart disease (RIHD), which contribute to deaths in this group [9,10]. According to respondents of a survey by The Council of Cardio-Oncology and the Council for Cardiology Practice, mainly from Europe, only 30% described themselves as experts in this field, while most rated their knowledge as sufficient. The respondents emphasized the absolute need for education on this topic [11].

Basic mechanisms of action of anticancer drugs (anthracyclines, trastuzumab, 5-fluorouracil, cyclophosphamide) and anthracycline-trastuzumab interaction

Anthracyclines

Anthracyclines are a group consisting of over 2000 derivatives. Many of these are anticancer drugs that are continuously refined by altering structural elements to find variants with the highest efficacy and the least harm to cardiomyocytes [12]. The primary mechanism of action is the stabilization of the topoisomerase-mediated cleavable complex. This stabilization results from the drug's strong binding to DNA, which can act as an apoptotic signal for the cancer cell. Indirect evidence suggests that the drug's effectiveness may be linked to the disruption of the quinone subunit reduction process, leading to the formation of a semiquinone radical. Additionally, the drug induces the production of a significant amount of reactive oxygen species, which also promotes cytotoxicity [13]. Anthracyclines have side effects, the cardiotoxic ones can result in heart failure [14].

Trastuzumab

Trastuzumab is an antibody directed against the epidermal growth factor receptor 2 (HER2), which consists of an extracellular ligand-binding domain, a transmembrane region, and an intracellular tyrosine kinase domain [15,16]. As an antibody, trastuzumab binds to the receptor through a mechanism called antibody-dependent cellular cytotoxicity [17]. It is estimated that 1%-4% of patients treated with trastuzumab may experience heart failure, and up to 10% of patients may experience reduced left ventricular ejection fraction [18]. The cardiotoxicity caused by trastuzumab can significantly amplify the damage previously induced by the use of anthracyclines, impairing the physiological mechanisms in the myocardium [19].

Fluorouracil

5-Fluorouracil exerts its antineoplastic effects by disrupting and consequently inhibiting thymidylate synthase and by interfering with the synthesis and function of nucleic acids [20]. It is suspected that coronary artery spasm leads to ischemic heart diseases associated with 5-fluorouracil. This spasm can occur through both endothelium-dependent and endothelium-independent mechanisms [21].

Cyclophosphamide

Cyclophosphamide is a cytostatic prodrug responsible for alkylating DNA, resulting in crosslinking RNA and DNA. Consequently, the proliferation of the cancer cell is halted due to the inhibition of protein synthesis [22,23]. Additionally, cyclophosphamide is an immunosuppressant that inhibits both humoral and cellular responses, making it useful in treating various autoimmune diseases. Cyclophosphamide used in cancer therapy comes in different concentrations. Cases of cardiotoxicity induced by it have been detected when the drug is used in high doses (<120 mg/kg) [24-26]. Acrolein and other metabolites of cyclophosphamide exert toxic effects on the myocardium by triggering reactive oxygen species and causing inflammation [26].

In **table 1**, drugs used in cancer therapy and their potential toxic effects are presented [27].

TABLE 1 Overview of drugs used in cancer therapy and their toxic effects

DRUG	TOXIC EFFECT
anthracyclines	Heart failure
Trastuzumab	Heart failure
5-fluorouracil	Dialeted cardiomiopathy, ventricular arrhythmia, sudden cardiac death
Cyclophosmphamide	Myocardium inflamation

Effects of radiotherapy on heart dysfunction

Cardiovascular complications caused by radiotherapy were first scientifically proven in 1978. A study involving 46 patients who underwent chest irradiation demonstrated that radiotherapy induced myocardial fibrosis, predominantly manifesting as clinical pericarditis [28]. Radiation-induced heart dysfunction is a significant issue faced by individuals who have survived thoracic cancers treated with radiotherapy [29]. While thoracic radiotherapy is an effective and beneficial treatment method for many malignancies, its association with myocardial dysfunction remains unclear [30]. Early radiation-induced disorders, often affecting the pericardium, typically present as acute pericarditis within weeks after treatment. Late complications within the thoracic region include coronary artery disease, chronic effusive pericarditis, constrictive pericarditis, and cardiomyopathy, appearing even up to 10 years post-treatment [31,32]. Due to substantial improvements in overall cancer survival rates, radiation-induced heart disease (RIHD) has become increasingly recognized as an adverse effect contributing to major complications of radiotherapy, including non-cancer-related deaths [33]. This is particularly significant in breast cancer or Hodgkin lymphoma patients, where long-term survival rates are high [31]. Structures of the heart, including the myocardium, pericardium, heart valves, capillaries, and conduction system, may sustain reversible or irreversible damage [34].

Pathophysiology of RIHD – radiation-induced heart disease

Radiation primarily acts through ionizing molecules in irradiated tissues, causing DNA damage. Radiation energy is directly absorbed, for example, in DNA, membranes, and organelles, or indirectly through the induction of reactive oxygen species (ROS) in the cytosol. Each cell generates approximately 10^5 ionizations when absorbing 1 Gray (1 Gy) of radiation. This results in about ~2000 single-strand breaks (SSBs), approximately 40 double-strand breaks (DSBs) in DNA, and other types of DNA damage [35]. Two mechanisms of radiation action can be distinguished: damaging cellular components through radiolysis products of water and direct ionization, as well as damaging cellular components through radiation itself [36]. Studies indicate that radiation-induced oxidative stress can stimulate the production of endogenous ROS in mitochondria, thereby activating p53. This leads to persistent mitochondrial dysfunction and genomic instability [37]. Excessive ROS and the regulation of PUMA (also known as bbc3), Bak, and Bax, dependent on p53, lead to increased mitochondrial membrane permeabilization, subsequent release of cytochrome c into the cytoplasmic matrix, activation of the apoptosome complex, and apoptosis induction [2]. Additionally, studies demonstrate a link between irradiation of human arteries and sustained inflammatory response associated with nuclear factor NF-κB activation. Research has also indicated that HOXA9 may be involved in regulating NF-κB activation [38]. Analyzing the transcription dynamics of TGF-beta 1 and type I and III procollagens in left ventricular cardiomyocytes after irradiation of rat hearts with doses of 15 Gy, 20 Gy, and 25 Gy in vivo, an increase in mRNA levels of TGF-beta 1 was observed. Single doses of 15 Gy and 20 Gy irradiation of the heart led to increased accumulation of von Willebrand factor [39]. It has been demonstrated that oxidative stress induced by various cytokines and growth factors, including TGF-β, TNF-α, IL-1, IL-11, CTGF, PDGF, VEGF, and FGF, contributes to fibrosis induction. Additionally, important mediators of cardiac fibrogenesis are factors belonging to the PDGF family [33]. Damage caused by ionizing radiation includes single-strand DNA breaks (SSBs), double-strand DNA breaks (DSBs), as well as various forms of DNA crosslinks and base damage [40]. Excess reactive oxygen species generate oxidative DNA damage, including oxidized bases and SSBs containing modified ends, which are repaired by the base excision repair (BER) pathway. Such damage activates DNA damage response (DDR) pathways, which are closely associated with telomere proteins and telomere maintenance [41]. Delayed chromosomal instability has been shown to result from telomere dysfunction following telomeric DNA damage [42]. Common telomeric damages include oxidative DNA damage, particularly 8-oxoguanine,

which plays a crucial role during replication fork stalling events [43]. Due to end replication problem, telomere length undergoes erosion with cell division. Incorporation of oxidized free deoxyribonucleoside triphosphates (dNTPs), especially 8-hydroxydeoxyguanosine (8-oxoG), by telomerase inhibits its activity and terminates telomere elongation. Consequently, permanent cell cycle arrest occurs, known as replicative senescence [44]. Introducing telomere length control as a prognostic factor for cardiovascular diseases will require precise quantitative measurement of telomere length [45]. Risk factors for developing heart dysfunction after radiotherapy depend on pre-existing risk factors. These include exposure to ionizing radiation at a young age, pre-existing heart diseases such as coronary artery disease, use of radiation fractions >2 Gy, and administration of cardiotoxic chemotherapeutics when radiation dose exceeds 30-40 Gy [34,46].

Classification of cardiotoxicity types associated with cancer therapy, based on therapy duration – mechanisms of cardiotoxicity

Cardiotoxicity (CTox) has long been recognized as a major side effect of chemotherapy in cancer patients [47]. Cardiotoxicity can manifest acutely during treatment or shortly after its completion and can be either transient or chronic, categorized into type I with early onset and type II with late onset [48]. Type I cardiotoxicity primarily involves irreversible cardiomyocyte loss and damage, while type II involves reversible/transient cellular dysfunction, such as mitochondrial and protein changes [49]. Type I cardiotoxicity can occur with anthracyclines, alkylating agents, or docetaxel, while type II can occur with agents like trastuzumab [50]. Cardiotoxicity induced by anthracyclines can lead to dilated and systolic heart failure (HF). For example, with doxorubicin, the risk of heart failure may be around 5% at a cumulative dose of 400 mg/m^2, increasing exponentially with higher doses [51]. The mechanism involves the binding of drug molecules with cardiolipins in the inner mitochondrial membrane, disrupting electron transport in the respiratory chain, leading to ATP depletion and decreased myocardial contractility. Additionally, these drugs contribute to the generation of free radicals and oxidative stress [32]. The doxorubicin-cardiolipin complex also generates hydroxyl radicals and hydrogen peroxide, further damaging cell membranes and DNA [31]. Nuclear factor erythroid 2 like 2 (Nrf2) acts as a sensor of oxidative stress, regulating responses to xenobiotic compounds. Nrf2 is negatively regulated by proteasomal degradation of Kelch Like ECH associated protein 1 (Keap1). Degradation of Keap1 leads to constitutive activation of Nrf2, enabling it to enter the nucleus and regulate antioxidant enzymes such as heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and glutathione S-transferase (GST) [52].

Impact of oncologic treatment methods on the cardiovascular system and strategies to mitigate these effects; examples of cardiovascular complications following oncologic treatment

As a result of the action of antineoplastic agents, significant episodes began to be observed regarding their impact on the cardiovascular system. Some of them are undesirable, and their nature is not favorable [53]. The consequences of treatment – complications – include myocardial dysfunction, including heart failure (HF). Particularly burdened with the risk of developing HF in the short term are elderly patients with pre-existing risk factors. For example, the incidence of HF in patients after treatment of aggressive non-Hodgkin lymphoma over a 5-year period reaches 17%. Complications after this treatment also include hypertension, arrhythmias, coronary artery, and valvular diseases [54]. 5-fluorouracil in the treatment of colorectal cancer may contribute to symptoms of angina pectoris and vasospasm, while VEGF-targeted anticancer tyrosine kinase inhibitors used in the same indication lead to life-threatening cardiovascular incidents (e.g., myocardial infarction or pulmonary embolism) with an incidence of 9.79%. Even selective cyclooxygenase-2 inhibitors used in cancer therapy to limit metastasis can lead to hypertension and thrombotic consequences as a result of atherosclerosis [55]. Cardiotoxicity is also a major limitation associated with the use of breast cancer therapy [56]. There are numerous discrepancies between guidelines on the care of patients taking potentially cardiotoxic antineoplastic drugs and those with developed complications in this area. In view of the above, specialists from the French Working Group have set out to systematize the recommendations of European and American societies [57]. For example, according to the recommendations, the treatment of myocarditis caused by immune checkpoint inhibitor (ICI) should be based on the cessation of ICI use, admission to the intensive care unit or cardiology department to confirm the suspicion, and simultaneous use of high doses of corticosteroids [58]. Pathology in the function of the heart ventricles, caused by the action of anthracyclines, can be limited in development by using angiotensin-converting enzyme inhibitors (ACEI) [59]. This is confirmed by Mozolevska et al. reporting on the impact of intervention in the RAS system on weakening heart function disorders in mice [60].

Knowledge of the effects of oncology treatment methods on the cardiovascular system contributes to enhancing treatment effects and reducing pauses in cancer therapy.

Risk factors

There are many risk factors that can contribute to both cardiovascular disease and cancer. These include primarily smoking and diabetes [61]. Diagnosis of cardiovascular disease is crucial in cancer patients as it plays a significant role in selecting therapies, which also demonstrate cardiotoxicity and affect patient prognosis [62]. Some studies have shown that pre-existing heart disease is associated with reduced chances of receiving anti-cancer therapies, including radiotherapy, chemotherapy, and surgeries, and with increased risk of death in lung cancer patients [63]. Another study indicated that in patients with Non-Hodgkin lymphoma, pre-existing cardiovascular disease is associated with increased risk of future heart failure [64].

Conclusions

There are some strong correlations indicating that both cardiac dysfunction prior and after cancer is a situation in which the treatments, as well as prognosis can differ from a heart dysfunction-free situation. A lot of drugs used in clinical practice as a cancer treatment can exacerbate the cardiotoxic effect of already existing cardiologic disease. The search for new drugs with maximum efficacy and minimal cardiotoxic component is necessary for better survival outcomes in patients experiencing cardiac pathologic activity, as well as cancer.

Ethical approval
This study is not related to either human or animal use.

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Not applicable.

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Conflict of interest
The authors declare no conflict of interest.

References

1. Araújo F, Gouvinhas C, Fontes F, La Vecchia C, Azevedo A, Lunet N. Trends in cardiovascular diseases and cancer mortality in 45 countries from five continents (1980-2010). Eur J Prev Cardiol. 2014;21(8):1004-17; DOI: 10.1177/2047487313497864.
2. Liang Z, He Y, Hu X. Cardio-oncology: mechanisms, drug combinations, and reverse cardio-oncology. Int J Mol Sci. 2022: 23(18):10617; DOI: 10.3390/ijms231810617.
3. Shi S, Lv J, Chai R, Xue W, Xu X, Zhang B, Li Y, Wu H, Song Q, Hu Y. Opportunities and challenges in cardio-oncology: a bibliometric analysis from 2010 to 2022. Curr Probl Cardiol. 2023;48(8):101227; DOI:10.1016/j.cpcardiol.2022.101227.
4. Kappel C, Rushton M, Johnson C, Aseyev O, Small G, Law A, Ivars J, Dent SF. Clinical experience of patients referred to a multidisciplinary cardio-oncology clinic: an observational cohort study. Curr Oncol. 2019;26(3):e322-7; DOI:10.3747/co.26.4509.
5. Burashnikov A, Abbate A, Booz GW. Cardiovascular complications of anticancer therapy: a developing storm in medicine. J Cardiovasc Pharmacol. 2022;80(4):491-2; DOI:10.1097/FJC.0000000000001355.
6. Han X, Zhou Y, Liu W. Precision cardio-oncology: understanding the cardiotoxicity of cancer therapy. NPJ Precis Oncol. 2017;1(1):31; DOI:10.1038/s41698-017-0034-x.
7. Lenneman CG, Sawyer DB. Cardio-oncology: an update on cardiotoxicity of cancer-related treatment. Circ Res. 2016;118(6):1008-20; DOI:10.1161/CIRCRESAHA.115.303633.
8. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, Cipolla CM. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. CA Cancer J Clin. 2016;66(4):309-25; DOI:10.3322/caac.21341.
9. Manrique CR, Park M, Tiwari N, Plana JC, Garcia MJ. Diagnostic strategies for early recognition of cancer therapeutics–related cardiac dysfunction. Clin Med Insights Cardiol. 2017;11:1179546817697983; DOI:10.1177/1179546817697983.
10. Ellahham S, Khalouf A, Elkhazendar M, Dababo N, Manla Y. An overview of radiation-induced heart disease. Radiat Oncol J. 2022;40(2):89-102; DOI:10.3857/roj.2021.00766.
11. Asteggiano R, Aboyans V, Lee G, Salinger S, Richter D. Cardiology care deliverd to cancer patients. Eur Heart J. 2020;41(2):205-6; DOI:10.1093/eurheartj/ehz935.
12. Bayles CE, Hale DE, Konieczny A, Anderson VD, Richardson CR, Brown KV, Nguyen JT, Hecht J, Schwartz N, Kharel MK, Amissah F, Dowling TC, Nybo SE. Upcycling the anthracyclines: New mechanisms of action, toxicology, and pharmacology. Toxicol Appl Pharmacol. 2023;459:116362; DOI:10.1016/j.taap.2022.116362.
13. Beretta GL, Zunino F. Molecular mechanisms of anthracycline activity. Top Curr Chem. 2008;283:1-19; DOI:10.1007/128_2007_3.
14. Volkova M, Raymond Russell I. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev. 2011;7(4):214-20; DOI:10.2174/157340311799960645.
15. Mohan N, Jiang J, Dokmanovic M, Wu WJ. Trastuzumab-mediated cardiotoxicity: current understanding, challenges, and frontiers. Antib Ther. 2018;1(1):13-7; DOI:10.1093/abt/tby003.
16. Boekhout AH, Beijnen JH, Schellens JHM. Trastuzumab. Oncologist. 2011;16(6):800-10; DOI:10.1634/theoncologist.2010-0035.
17. Vu T, Claret FX. Trastuzumab:updated mechanisms of action and resistance in breast cancer. Front Oncol. 2012;2:62; DOI:10.3389/fonc.2012.00062.
18. Jawa Z, Perez RM, Garlie L, Singh M, Qamar R, Khandheria BK, Jahangir A, Shi Y. Risk factors of trastuzumab-induced cardiotoxicity in breast cancer: a meta-analysis. 2016;95(44):e5195; DOI:10.1097/MD.0000000000005195.
19. Nicolazzi MA, Carnicelli A, Fuorlo M, Scaldaferri A, Masetti R, Landolfi R, Favuzzi AMR. Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer. Eur Rev Med Pharmacol Sci. 2018;22(7):2175-85; DOI:10.26355/eurrev_201804_14752.
20. Zhang N, Yin Y, Xu SJ, Chen WS. 5-Fluorouracil: mechanisms of resistance and reversal strategies. Molecules. 2008;13(8):1551-69; DOI:10.3390/molecules13081551.
21. Sara JD, Kaur J, Khodadadi R, Rehman M, Lobo R, Chakrabarti S, et al. 5-fluorouracil and cardiotoxicity: a review. Ther Adv Med Oncol. 2018;10:1758835918780140; DOI:10.1177/1758835918780140.
22. Christine M. Stork, Susan M. Schreffler. Cyclophosphamide. In: Wexler P, editor. Encyclopedia of toxicology, 4th ed. Science Direct: Academic Press; 2024. p. 417-421.
23. Voelcker G. The real mechanism of action of cyclophosphamide and other oxazaphosphorine cytostatics. Japan J Res. 2020;1(2):1-2; DOI: 10.33425/2690-8077.1007.
24. Winkelstein A. Mechanisms of immunosuppression: effects of cyclophosphamide on cellular immunity. Blood. 1973;41(2):273-84; DOI:10.1182/blood.V41.2.273.273.
25. Madondo MT, Quinn M, Plebanski M. Low dose cyclophosphamide: mechanisms of T cell modulation. Cancer Treat Rev. 2016;42:3-9; DOI:10.1016/J.CTRV.2015.11.005.
26. Kamel SS, Abdelbaky NA, Sayed-Ahmed MM, Karkeet RM, Osman AMM, Fouad MA. Cyclophosphamide-induced cardiotoxicity. Azhar Inter J Pharm Med Sci. 2022;2(2):1-8; DOI:10.21608/AIJPMS.2022.114213.1103.
27. Rawat PS, Jaiswal A, Khurana A, Bhatti JS, Navik U. Doxorubicin-induced cardiotoxicity: an update on the molecular mechanism and novel therapeutic strategies for effective management. Biomed Pharmacother. 2021;139:111708; DOI:10.1016/j.biopha.2021.111708.
28. Nabiałek-Trojanowska I, Lewicka E, Wrona A, Kaleta AM, Lewicka-Potocka Z, Raczak G, Dziadziuszko R. Cardiovascular complications after radiotherapy. Cardiol J. 2020;27(6):836-47; DOI:10.5603/CJ.a2018.0120.
29. Pedersen LN, Schiffer W, Mitchell JD, Bergom C. Radiation-induced cardiac dysfunction: Practical implications. Kardiol Pol. 2022;80(3):256-65; DOI:10.33963/KP.a2022.0066.
30. Nolan MT, Russell DJ, Marwick TH. Long-term risk of heart failure and myocardial dysfunction after thoracic radiotherapy: a systematic review. Can J Cardiol. 2016;32(7):908-20; DOI:10.1016/j.cjca.2015.12.020.

31. Młot B, Rzepecki P. Kardiotoksyczność leczenia onkologicznego. Nowotwory J Oncol. 2010;60(6):536-547.
32. Kucharska W, Negrusz-Kawecka M, Gromkowska M. Cardiotoxicity of oncological treatment in children. Adv Clin Exp Med. 2012;21(3):281-8.
33. Zou B, Schuster JP, Niu K, Huang Q, Rühle A, Huber PE. Radiotherapy-induced heart disease: a review of the literature. Precis Clin Med. 2019;2(4):270-82; DOI:10.1093/pcmedi/pbz025.
34. Geiger S, Lange V, Suhl P, Heinemann V, Stemmler HJ. Anticancer therapy induced cardiotoxicity: review of the literature. Anticancer Drugs. 2010;21(6):578-90; DOI:10.1097/CAD.0b013e3283394624.
35. Minniti G, Goldsmith C, Brada M. Radiotherapy. Handb Clin Neurol. 2012;104:215-28; DOI:10.1016/B978-0-444-52138-5.00016-5.
36. Gramatyka M. Cardiotoxicity as undesired side effect in the treatment of breast cancer. Postepy Hig Med Dosw. 2014;68:483-97; DOI:10.5604/17322693.1101581.
37. Kuribayashi K, Finnberg N, Jeffers JR, Zambetti GP, El-Deiry WS. The relative contribution of pro-apoptotic p53-target genes in the triggering of apoptosis following DNA damage in vitro and in vivo. Cell Cycle. 2011;10(14):2380-9; DOI:10.4161/cc.10.14.16588.
38. Filopei J, Frishman W. Radiation-induced heart disease. Cardiol Rev. 2012;20(4):184-8; DOI:10.1097/CRD.0b013e3182431c23.
39. Przybyszewski WM, Wideł M, Rzeszowska-Wolny J. Kardiotoksyczne nastepstwa promieniowania jonizujacego i antracyklin. Postepy Hig Med Dosw. 2006;60:397-405.
40. Merrifield M, Kovalchuk O. Epigenetics in radiation biology: a new research frontier. Front Genet. 2013;4(4):40; DOI:10.3389/fgene.2013.00040.
41. Shim G, Ricoul M, Hempel WM, Azzam EI, Sabatier L. Crosstalk between telomere maintenance and radiation effects: a key player in the process of radiation-induced carcinogenesis. Mutat Res. 2014;760:1-17; DOI:10.1016/j.mrrev.2014.01.001.
42. McKenna MJ, Bailey SM. Chromosomal and telomeric biomarkers of normal tissue injury to evaluate risk of degenerative health effects (secondary malignancy, cardiovascular disease) post radiation therapy. Transl Cancer Res. 2017;6(5):789-94; DOI:10.21037/tcr.2017.05.20.
43. Coluzzi E, Leone S, Sgura A. Oxidative stress induces telomere dysfunction and senescence by replication fork arrest. Cells. 2019;8(1):19; DOI:10.3390/cells8010019.
44. Luxton JJ, McKenna MJ, Taylor LE, George KA, Zwart SR, Crucian BE, Drel VR, Garrett-Bakelman FE, Mackay MJ, Butler D, Foox J, Grigorev K, Bezdan D, Meydan C, Smith SM, Sharma K, Mason CE, Bailey SM. Temporal telomere and DNA damage responses in the space radiation environment. Cell Rep. 2020;33(10):108435; DOI:10.1016/j.celrep.2020.108435.
45. M'kacher R, Girinsky T, Colicchio B, Ricoul M, Dieterlen A, Jeandidier E, Heidingsfelder L, Cuceu C, Shim G, Frenzel M, Lenain A, Morat L, Bourhis J, Hempel WM, Koscielny S, Paul JF, Carde P, Sabatier L. Telomere shortening: a new prognostic factor for cardiovascular disease post-radiation exposure. Radiat Prot Dosimetry. 2015;164(1-2):134-7; DOI:10.1093/rpd/ncu296.
46. Bovelli D, Plataniotis G, Roila F. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO clinical practice guidelines. Ann Oncol. 2010;21(5): v277-82; DOI:10.1093/annonc/mdq200.
47. López-Sendón J, Álvarez-Ortega C, Zamora Auñon P, Buño Soto A, Lyon AR, Farmakis D, Cardinale D, Canales Albendea M, Feliu Batlle J, Rodríguez Rodríguez I, Rodríguez Fraga O, Albaladejo A, Mediavilla G, González-Juanatey JR, Martínez Monzonis A, Gómez Prieto P, González-Costello J, Serrano, Antolín JM, Cadenas Chamorro R, López Fernández T. Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: the CARDIOTOX registry. Eur Heart J. 2020;41(18):1720-9; DOI:10.1093/eurheartj/ehaa006.
48. Dong J, Chen H. Cardiotoxicity of anticancer therapeutics. Front Cardiovasc Med. 2018;5(9); DOI:10.3389/fcvm.2018.00009.
49. Curigliano G, Cardinale D, Suter T, Plataniotis G, De azambuja E, Sandri MT, Criscitiello C, Goldhirsch A, Cipolla C, Roila F. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. Ann Oncol. 2012;23(7):vii155-66; DOI:10.1093/annonc/mds293.
50. Korzeniowska K, Cieślewicz A, Jankowski J, Neumann D, Jabłecka. Powikłania sercowo-naczyniowe leczenia onkologicznego. Farmac Wspol. 2016;9:189-93;
51. Menna P, Salvatorelli E. Primary prevention strategies for anthracycline cardiotoxicity: a brief overview. Chemotherapy. 2017;62(3):159-68; DOI:10.1159/000455823.
52. Kong CY, Guo Z, Song P, Zhang X, Yuan YP, Teng T, Yan L, Tang QZ. Underlying the mechanisms of doxorubicin-induced acute cardiotoxicity: oxidative stress and cell death. Int J Biol Sci. 2022;18(2):760-70; DOI:10.7150/ijbs.65258.
53. Tajiri K, Aonuma K, Sekine I. Cardiovascular toxic effects of targeted cancer therapy. Jap J Clin Oncol. 2017;47(9):779-85; DOI:10.1093/jjco/hyx071.
54. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM, 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;37(36):2768-801; DOI:10.1093/eurheartj/ehw211.
55. Georgiyeva K, Blake P. Medical sciences – cardiovascular side effects of colon cancer therapy. Sci Eur. 2022;99:20-4; DOI:10.5281/zenodo.7014308.
56. Bikiewicz A, Banach M, von Haehling S, Maciejewski M, Bielecka-Dabrowa A. Adjuvant breast cancer treatments cardiotoxicity and modern methods of detection and prevention of cardiac complications. ESC Heart Fail. 2021;8(4):2397-418 DOI:10.1002/ehf2.13365.
57. Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem JE, Barlesi F, Farnault L, Charbonnier A, Mirabel M, Champiat S, Cohen-Solal A, Cohen A, Dolladille C, Thuny F. Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the american and european cardio-oncology guidelines. J Am Heart Assoc. 2020;9(18); DOI:10.1161/JAHA.120.018403.
58. Thuny F, Alexandre J, Salem JE, Mirabel M, Dolladille C, Cohen-Solal A, Cohen A, Ederhy S, Cautela J. Management of immune checkpoint inhibitor-induced myocarditis: the French Working Group's Plea for a pragmatic approach. JACC CardioOncol. 2021;3(1):157-61; DOI:10.1016/j.jaccao.2020.12.001.
59. Ananthan K, Lyon AR. The role of biomarkers in cardio-oncology. J Cardiovasc Transl Res. 2020;13(3):431-50; DOI:10.1007/s12265-020-10042-3.
60. Beyer AM, Bonini MG, Moslehi J. Cancer therapy-induced cardiovascular toxicity: old/new problems and old drugs. Am J Physiol Heart Circ Physiol. 2019;317:164-7; DOI:10.1152/ajpheart.00277.2019.
61. Guo J, Fang P, Shi W, Luo P, Huo S, Yan D, Wang M, Peng D, Men L, Li S, Lv J, Lin L. Preexisting cardiovascular risk factors and coronary artery atherosclerosis in patients with and without cancer. Cardiol Res Pract. 2022;2022:4570926; DOI: 10.1155/2022/4570926.
62. Mamas MA, Matetic A. How common is pre-existing cardiovascular disease in cancer patients: what do we know? Does it matter? JACC Cardioɛ Oncol. 2022;4(2):254-7; DOI:10.1016/j.jaccao.2022.05.001.
63. Batra A, Sheka D, Kong S, Cheung WY. Impact of pre-existing cardiovascular disease on treatment patterns and survival outcomes in patients with lung cancer. BMC Cancer. 2020;20(1):1004; DOI:10.1186/s12885-020-07487-9.
64. Salz T, Zabor EC, Brown P de N, Dalton SO, Raghunathan NJ, Matasar MJ, Steingart R, Vickers AJ, Munksgaard PS, Oeffinger KC, Johanses C. Preexisting cardiovascular risk and subsequent heart failure among non-hodgkin lymphoma survivors. J Clin Oncol. 2017;35(34):3837-43; DOI:10.1200/JCO.2017.72.4211.