AN OVERVIEW OF PHARMACOLOGICAL AND NON-PHARMACOLOGICAL TREATMENT AS A USEFUL TOOL FOR THE PROTECTION FROM CARDIOTOXICITY OF ANTINEOPLASTIC DRUGS

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PREGLED FARMAKOLOŠKIH I NEFARMAKOLOŠKIH TRETMANA U PREVENCIJI KARDIOTOKSIČNOSTI USLED PRIMENE ANTINEOPLASTIČNIH LEKOVA

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ABSTRACT

Unfortunately, in patients with cancer disease, clinical application of antineoplastic drug results in severe side effects of cardiotoxicity.

We aim to review the research focused on elimination or reduction of antineoplastic drug-induced cardiotoxicity without affecting its anticancer efficacy by different agens.

This study is based on pertinent papers that were retrieved by a selective search using relevant keywords in PubMed and ScienceDirect. Based on mentioned purpose, various strategies were investigated and proposed, and thousands of compounds were screened. The literature mainly focusing on drugs, natural products and herb extracts with therapeutic efficacies as well as non-pharmacological treatment against differently induced cardiotoxicity during treatment in patients with cancers.

Larger future studies are necessary to reach a point of secure cytostatic therapy, improved patient survival and quality of life. Until that moment, baseline and serial cardiac evaluation is recommended to facilitate early identification and treatment of cardiotoxicity.

Keyword: *cardiotoxicity, anti-neoplastic therapy, pharmacological, herbal, natural cardioprotection, physical exercise, heart.*

SAŽETAK

Nažalost, kod pacijenata sa obolelih od karcinoma, klinička primena antineoplastičnih lekova rezultiraozbiljnim neželjenim efektima i kardiotoksičnošću.

Cilj ovog preglednog rada je sveobuhvatan prikaz informacija a koje su usmerene na eliminaciju ili smanjenje kardiotoksičnosti izazvane antineoplastičnim lekovima i bez uticaja na njegovu efikasnost protiv raka različitim agensima.

Ova studija zasnovana je na relevantnim i dostupnim radovima koji su preuzeti selektivnom pretragom koristeći relevantne ključne reči u PubMed i ScienceDirect-u. U vezi sa ciljem rada, u prethodnim studijama istražene su i predložene razne strategije, a na hiljade jedinjenja je prikazano. Literaturni podaci se fokusiraju na lekove, prirodne proizvode i ekstrakte biljaka sa terapijskim efektima, kao i na nefarmakološkom tretmanu indukovane kardiotoksičnosti tokom lečenja kod pacijenata sa kancerom.

Opsežnije buduće studije su neophodne da bi se postigla tačka sigurne citostatske terapije, bolje opšte stanje pacijenta i kvalitet života. Do tog trenutka, preporučuje se osnovna i obavezna procena funkcije srca kako bi se olakšala rana identifikacija i lečenje kardiotoksičnosti.

Ključne reči: *kardiotoksičnost, anti-neoplastična terapija, farmakološka, biljna, prirodna kardioprotekcija, vežbanje, srce.*

INTRODUCTION

Last decades, cancer has become one of the leading causes of death worldwide in both sexes, with significant geographic variations in frequency and distribution. In 2012, an estimated 14.1 million new cases of cancer occurred worldwide and worldwide there will be 23.6 million new cases of cancer each year by 2030 (1). According to previosly published epidemiology results, Serbia is the country with the highest cancer mortality in the world last years. In the period from 1991 to 2015, approximately 266,000 males and 200,000 females died from cancer in Serbia (2).

In that sense, recently data emphaze that the 28% of patients diagnosed with cancer (all cancers combined) in England in 2013-2014 had curative or palliative chemotherapy, as part of their primary cancer treatment (2). This includes patients who had chemotherapy alone, and those

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Table 1. Antineoplastic Agents Associated With Cardiotoxicity (4, 5, 7-9, 12, 13).

Antineoplastic agent	*Major cardiac side effect*	*Incidence*
Daunorubicin/doxorubicin	*Acute/chronic CHF*	*18%–65%*
Cyclophosphamide/ifosfamide	*Myocarditis, CHF*	*17%-25%*
Paclitaxel/docetaxel	*Hypotension, hypertension, bradycardia, atrial and ventricular arrhythmia*	*0.5%*
Fluorouracil	*MI,angina, hypotension, coronary vasospasm*	*1.6%–68%*
Rituximab	*Hypotension, hypertension, arrhythmia*	*25%*
Arsenic trioxide	*QT prolongation, tachycardia*	*8%–55%*
Trastuzumab	*CHF*	*7%–28%*
Bevacizumab	*CHF*	*4%-6%*
Etoposide	*MI, hypotension*	*1%–2%*
Vinca alkaloids	*MI,autonomic cardioneuropathy*	*25%*
Pentostatin	*MI, CHF, acute arrhythmia*	*3%-10%*
Cytarabine	*Arrhythmia, pericarditis, CHF*	*Unknown*
Interferon (at high doses)	*Arrhythmia, dilated cardio-myopathy, ischemic heart disease*	*Unknown*
Busulfan	*Endocardial fibrosis*	*Unknown*
Cisplatin	*Acute MI*	*Unknown*
Thalidomide	*Pulmonary hypertension*	*Unknown*

who also had other treatments such as tumour removal surgery or radiotherapy (3).

Because of widely used drugs, it is important to patients well enought tolerate the treatment. More than 100 chemotherapy or chemo drugs are used to treat cancer – either alone or in combination with other drugs or treatments. These drugs are very different in their chemical composition, how they are taken, their usefulness in treating specific forms of cancer, and their side effects (4). Cancers treatment by chemo-drug induce different side effects on various organ system, from central nervous to cardiovascular, gastrointestinal, skin to fertility and endocrinological problems (5, 6).

This review is aimed to introduces and briefly summarizes the information about present and possible pharmacological and non-pharmacological treatment as a useful tool to for the protection from chemotherapeutic drug-indiced cardiotoxicity.

Cardiac toxicity as an chemo-drug`s side effect: Incidence, Pathophysiology and Mechanisms

An ever-increasing array of chemotherapeutic agents is being used in the treatment of solid organ or hematologic malignancies. The success of many of these agents has led to an increasing survival of patients with cancer. However, many of these agents, particularly anthracyclines and trastuzumab, are associated with the development of cardiotoxicity (6, 7).

Cardiotoxicity is one of the most important adverse reactions of chemotherapy, leading to an important increase of morbidity and mortality (7, 8). The most studied chemotherapeutic agents associated with adverse cardiac events are anthracyclines (Doxorubicin), used in the treatment of many adult malignancies like breast cancer, sarcoma, lymphoma, or gynecological cancer. They also play an important role in the treatment of childhood cancers, anthracyclines are currently used in more than 50% of regimens contributing to the overall survival rates in excess of 75% (6-8). Other cytostatics more frequently correlated with cardiotoxic side effects are taxanes (paclitaxel, docetaxel), alkylating agents (Carboplatin, Cisplatin, Cyclophosphamide), small molecule tyrosine kinase inhibitors (lapatinib, imatinib, sorafenib, sunitinib) and trastuzumab, a monoclonal antibody directed against the human epidermal growth factor receptor-2 (HER2), used in the treatment of metastatic breast neoplasm (Table 1).

Cardiotoxicity can appear early or late in the course of the disease, and may vary from subclinical myocardial dysfunction to irreversible heart failure or even death (9). This definition refers to a direct effect of the chemotherapy on the entire cardiovascular system, but also to an indirect effect due to a thrombogenic status or to a hemodynamic flow alteration (10-13).

A committee of the cardiac review and evaluation supervising trastuzumab clinical trials clinically defined chemotherapy-induced cardiotoxicity as one or more of the following: 1) reduction of LVEF, either global or specific in the interventricular septum; 2) symptoms or signs associated with heart failure (HF); 3) reduction in LVEF from baseline ≤ to 5% to <55% in the presence of signs or symptoms of HF, or a reduction in LVEF ≥10% to <55% without signs or symptoms of HF (9-13).

Accumulated data revealed that oxidative stress, iron metabolism, inflammation, and other mechanisms participate in this multifactorial process. A hallmark of anthracycline-induced chronic cardiotoxicity is the reduction of left ventricular wall thickness due to the loss of cardiomyocytes, resulting in restricted LVEF. Anthracycline-induced cardiomyocyte cell death is likely mediated through caspase-3-related apoptotic pathways activated by p53 and/or TNF-signalling (11). The trigger stimuli ultimately causing cardiomyocyte cell death are uncertain and controversially discussed. Suggested mechanisms for the development of cardiomyopathy include accumulation of toxic metabolites (e.g., doxorubinicol), autophagy, production of peroxynitrite and ROS, TOP2B inhibition, and disruption of mitochondrial homeostasis/integrity (12, 13).

Pharmacological treatment of chemotherapeutic-induced cardiotoxicity

Dexrazoxane

Dexrazoxane is a cardioprotective agent which was discovered by Kurt Hellmann in 1972 (14). In July 2011 the US Food and Drug Administration released a statement restricting use only in adult patients with cancer who have received >300 mg/m^2 doxorubicin or >540 mg/m^2 epirubicin and general approval for use for cardioprotection (14). As the use of the only clinically approved cardioprotectant dexrazoxane has been limited, there is an urgent need for alternative cardioprotective measures. Approved indication for its use is extravasation of anthracyclines, and because the number of patients who have extravasation of anthracyclines is low, the condition is considered 'rare', dexrazoxane was designated an 'orphan medicine' (15).

As a derivative of ethylene diamine tetra acetic acid (EDTA), dexrazoxane chelates iron and thus reduces the number of metal ions complexed with anthracycline and, consequently, decrease the formation of superoxide radicals (16). The exact chelation mechanism is unknown, but it has been postulated that dexrazoxane can be converted into ring-opened form intracellularly and interfere with iron-mediated free radical generation that is in part thought to be responsible for anthracycline induced cardiomyopathy (16, 17).

Renin-angiotensin-aldosterone system antagonists

RAS involvement in the pathophysiology of chemotheraputic drug-mediated cardiac dysfunction has raised the question as to whether the prophylactic use of RAS antagonists could potentially mitigate these cardiotoxic effects. Previous basic science studies have demonstrated that the prophylactic administration of angiotensin converting enzyme inhibition (ACEI), including Captopril, Enalapril, and Lisinopril, was partially cardioprotective in both acute and chronic animal models of DOX induced cardiomyopathy (18, 19). In a rabbit model of DOX mediated cardiomyopathy, 1 mg/kg/day oral Lisinopril for a total of 10 weeks attenuated cardiomyocyte loss and ANP mRNA expression, in comparison to rabbits receiving DOX alone (20). Furthermore, intragastric administration of Captopril (10 mg/kg) or Enalapril (2 mg/kg) for 7 days resulted in a decline in lipid peroxidation, and enzymatic indicators of acute cardiac toxicity in a rat model of DOX induced cardiomyopathy (20, 21).

The therapeutic benefit closely depends on the improvement of left ventricular function. The ACE inhibitor enalapril and the beta-blocker carvedilol are the most effective drugs in achieving normalization of anthracycline-caused decrease in LVEF. Due to these promising therapeutic results, a preventive study was initiated. In the OVERCOME trail, 42% of the patients showed a preservation of LVEF by prophylactic enalapril and carvedilol treatment, and 10% of patients responded partially (22). However, these cardioprotective effects are less marked than in the case of dexrazoxane-based prevention.

Statins

Besides the most common hypothesis that anthracycline-induced congestive heart failure (CHF) is mainly caused by generation of reactive oxygen species (7-11), recent data point to a critical role of topoisomerase II beta (TOP2B), which is a primary target of anthracycline poisoning, in the pathophysiology of CHF (12, 14). Statins are anti-inflammatory and anti-oxidative drugs that are clinically well established for the prevention of cardiovascular diseases. They exhibit pleiotropic beneficial properties beyond cholesterol-lowering effects that most likely rest on the indirect inhibition of small Ras homologous (Rho) GTPases. The Rho GTPase Rac1 has been shown to be a major factor in the regulation of the pro-oxidative NADPH oxidase as well as in the regulation of type II topoisomerase.

Riad et al. suggested both anti-oxidative and anti-inflammatory effects of statins to contribute to cardioprotection. The statin enhanced SOD_2 levels, reduced caspase-3-mediated apoptosis and mitigated cardiac inflammation following doxorubicin treatment (23). Regarding their anti-inflammatory properties, statins, predominately atorvastatin, simvastatina and rosuvastatin, are described to inhibit nuclear translocation of Nf-kappaB by RhoA/ROCK inhibition, in vitro (24). Huelsenbeck et al demonstrated that a statin co-treatment attenuates acute anthracycline-induced cardiotoxicity in BALB/c mice as mirrored by reduced mRNA levels of pro-fibrotic and pro-inflammatory cytokines. It also protected from doxorubicin-induced sub-acute cardiac damage (25). In a similar study, atorvastatin protected mice from doxorubicin-induced DNA damage, lipid peroxidation and glutathione depletion (26).

Taken together, attenuation of Rho GTPase signalling seems to mainly contribute to the anti-atherosclerotic properties of statins and might also be of relevance beyond the maintenance of cardiovascular health (27).

β-blockers

Non-selective beta blockers (metoprolol, carvedilol and nebivolol) are cardioprotective drugs which could be effective into prevent chemotherapy-induced left ventricular systolic dysfunction (LVSD) in patients with hematological malignancies. In a randomized controlled trial of 50 patients in whom anthracycline therapy was planned, a 10% drop in LVEF occurred in most of the 25 placebo recipients in the study, although LVEF remained >50% in many of them. LVEF was preserved in the vast majority of the 25 patients randomized to receive carvedilol, demonstrating its protective effect. LVEF declined to <50% in only one carvedilol patient but in five of the controls (28).

This finding was confirmed in a later study randomizing patients to carvedilol and enalapril or placebo prior to starting anthracycline-based therapies. A significantly lower rate of death, heart failure, or final LVEF <45% occurred among the group receiving dual therapy versus placebo (6.7% versus 24.4%, p=0.02) (29). In the largest clinical trial of β-blockers for prevention of cardiotoxicity conduceted by Mônica Samuel et al (30), under contemporary anthracycline chemotherapy dosage, the authors noted a 13.5% to 14.5% incidence of cardiotoxicity. In this scenario, carvedilol had no impact on the incidence of early onset of LVEF reduction. However, the use of carvedilol resulted in a significant reduction in troponin levels and diastolic dysfunction (30, 31). The benefit of the use of pre-chemotherapy beta-blockers for prevention of chemo-induced cardiotoxicity remains unclear still. It is possible that the anti-oxidant effects of specific beta-blockers is what is preventing the toxic effects of anthracyclines/trastuzumab and not the beta-blockade itself.

Calcium channel blockers

Calcium channel blockers have a various potential beneficial effect which could be a treatment tool in preventing of cardiotoxicity induced by antineoplastic drugs. Well, we know that these drugs induce vasodilation of blood vessels and have anti-ischemic potential. Because of that, in an attempt to reduce the adverse cardiac effects, prophylaxis with a calcium channel blocker was therefore tested in a similar group of patients receiving similar induction chemotherapy.

Calcium channel blockers have previously been used as prophylaxis during 5-fluorouracil (5-FU) treatment only in a limited number of patients. These attempts have so far yielded conflicting results. A combination of nifedipine and isosorbide-dinitrate was found ineffective in the prevention of 5-FU cardiotoxicity in two patients reported by Escudier et al (32). Furthermore, verapamil did seem to modify the adverse cardiac effects of 5-FU by preventing arrhythmia (32). Also, one key and simple approach to monitor the effects of chemotherapy is arterial pressure measurement to identify hypertension. Hypertension is frequently seen in patients who are treated with several antiangiogenic agents (such as bevacizumab, sorafenib, and sunitinib) and can be severe (33). Hypertension in the cancer patient under therapy needs to be promptly and adequately treated, and calcium channel blockers can be a potential preventive therapy (33).

Natural and herbal products as treatment of chemotherapeutic-induced cardiotoxicity

As is known, antioxidants may neutralize free radicals generated by anthracyclines and potentially reduce cardiotoxicity. In that sense, natural antioxidants such as vitamin E, vitamin C, carotenoids,vitamin A, coenzyme Q, flavonoids, antioxidant components of virgin olive oil and selenium from plants are in focus laste decades in preventing of cardiovascular disorders.

Vitamin E and A as an antioxidants can protect from both acute and chronic cardiotoxicity caused by DOX, and it increases antioxidant capacity in the heart. With the aim of testing the cardioprotective effect of vitamin E in doxorubicin- induced acute cardiotoxicity in rats, Puri et al pretreated them with a high dose of vitamin E intraperitoneally followed by DOX (34).

The results show that vitamin E pre-treatment prevents the electrocardiographic changes caused by doxorubicin; moreover, it helps to lower the levels of creatine phosphokinase and lactate dehydrogenase raised by DOX. At high doses (>90 mg/kg), vitamin E also reduces lipid peroxidation and chromosomal aberrations (34).

Vitamin C (ascorbic acid) is an effective water soluble antioxidant against lipid peroxidation, scavenging ROS in the aqueous fraction before these molecules can give rise to lipid oxidation. Vitamin A and C also have a protective dose-dependent effect against the chromosomal aberrations induced by doxorubicin (35, 36).

Coenzyme Q (CoQ), or ubiquinone, plays a critical role in the mitochondrial respiratory chain, acting as a redox link between flavo-proteins and cytochromes, being an essential component in extramitochondrial redox chains. Its concentration in blood and tissues depends on biologic requirements, endogenous biosynthesis, and of course the dietary intake. Preclinical studies have shown that both supplementation and treatment with CoQ10 prior to DOX administration decreases lipid oxidation and heart toxicity without interfering with the anti-tumour activity of DOX. Clinical studies have also shown oral CoQ10 to have a protective effect against the chronic cardiotoxicity induced by anthracyclines (37, 38).

Flavonoids, polyphenols, and other natural antioxidants also is investigated as a potential beneficial factors in preventing various drug induced-cardiotoxicity. Flavonoids are characterized by high antioxidant power, and have been considered potential protectors against the chronic cardiotoxicity associated with DOX This protective effect of flavonoids is closely related to their antioxidant, iron chelating and carbonyl reductase 1 (CBR1)-

inhibitory properties (39). The flavonoid inhibits negative cardiac effects in a dose-dependent manner, in accordance with the essential properties of all flavonoids, i.e. their iron chelating and antioxidant characteristics (39, 40).

Other flavonoids, such as catechins, have cardioprotective properties at low doses, exhibiting an iron chelating activity. Quercetin, in addition to its high antioxidant capacity, can inhibit TOP2 and intercalate into DNA strands, thereby boosting the anti-tumour effect. Oral garlic supplementation decreases the oxidative stress provoked by chronic administration of DOX, and protects against free radicals, improving the clinical efficacy of adriamycin (41). Moreover, chronic garlic administration (250 and 500 mg/kg daily, orally, for 30 days) has been shown to prevent acute adriamycin- induced cardiotoxicity and decreases myocardial TNFa expression (42).

Furthermore, genistein, a soy isoflavone with high antioxidant capacity, can increase cellular antioxidant status by scavenging ROS and augmenting the activity of antioxidant enzymes like glutathione peroxidase, glutathione reductase (43).

The protective role of resveratrol, polyphenolic compound against DOX cardiotoxicity is being studied. It is known that pre-treatment with resveratrol and subsequent treatment with doxorubicin in H9c2 cardiomyocytes protects against the toxicity generated by DOX and can decrease the intracellular accumulation of ROS induced by xanthine oxidase/ xanthine (44).

Weak protective activity of selenium has also been reported against the nephrotoxicity (46) and hepatotoxicity (45) induced by DOX in rats. Finally, a recent study shows that a commercial mixture of vitamins (C, E and b-carotene) and minerals (copper, selenium and zinc) administered to Drosophila melanogaster larvae treated with DOX, was not genotoxic and it also protected against the genotoxic effects of chemotherapeutic agents (45, 46).

This cardioprotective effect of oleuropein (47) and curcumin (48) also was investigated, and results indicate that these agents could be beneficial in CVD-preventing, but further investigations are necessary to confirm this.

Non-Pharmacological treatment of chemotherapeutic-induced cardiotoxicity

Hyperbaric oxygen therapy (HBOT)

The relatively high levels of oxygen deliverable with HBO make this approach attractive, and the results of many studies support the hypothesis that HBO reduces the radioresistance of certain types of tumors. So, it is very difficult to find clear borderline between toxic and preventive dose od oxygen in patients with antioneplastic drugs treatment. Hyperbaric oxygen (HBO) therapy was studied in two animal models. In one animal study HBO was found to potentiate the cytotoxicity of doxorubicin due to its free-radical formation properties (49). The second animal study showed a beneficial effect in ulcer healing compared to mice that received no HBO therapy (50).

Karagoz et al investigated the effects of HBOT on DOX-induced cardiotoxicity in rats. Well, Wistar rats were treated with either HBO2 or doxorubicin or a combination of both treatments for 4 consecutive weeks and followed up for an additional 4 weeks. Cardiomyopathy was evaluated using two-dimensional and M-mode echocardiography at baseline, at the fourth, sixth and eighth weeks, and by histopathological investigation of the rat hearts at the eighth week. The concluded that HBOT markedly reduced ejection fraction and fractional shortening, this reduction was significantly less than that of doxorubicin treatment and attenuated doxorubicin-induced histopathological changes in rat hearts (51).

Other studies, concluded that HBO_2 therapy does not potentiate doxorubicin-induced cardiotoxicity in rats and that potential cardioprotection conferred by HBO_2 against doxorubicin warrants further investigation (51, 52).

Physical exercise

Regular and vigorous physical exercise has been scientifically established as providing strong preventative medicine against cancer with the potential to reduce incidence by 40% (53). It is well established that exercise capacity is an important prognostic factor for survival in cancer and non-cancer populations (53, 54).

There has been growing interest in evaluating the benefits of exercise training to improve oncologic outcomes. The use of exercise therapy to reduce cardiotoxicity in patients undergoing chemotherapy has yielded mixed results. Potential mechanisms by which exercise influence on cardiac function are mitigates the multiple molecules and signaling pathways, such as oxidative stress, iron metabolism, and inflammation, which are associated with chemotherapeutic drug -induced cardiotoxicity (53).

In a prospective study, 2973 women undergoing treatment for nonmetastatic breast cancer were asked to complete a questionnaire about their leisure time physical activity (55). Women who exercised for ≥9 metabolic equivalent task (MET)-hours/week had a 23% reduction in the risk of cardiovascular events, including heart failure, compared to those who exercised <9 MET-hours/week. Conversely, an uncontrolled study showed that aerobic exercise as an adjunctive therapy with trastuzumab did not prevent left ventricular dilation or a reduction in LVejection fraction (56).

Physical exercise at different intensities performed before, during, or after chemotherapy treatment increases cardiovascular reserve, reduces cardiotoxicity in mouse models,and increases peak Vo2 in patients treated with doxorubicin and cyclophosphamide (55, 56). However, a small study reported no beneficial effects on LVEF during adjuvant trastuzumab treatment (57). Ongoing small trials are currently studying the effect of different levels of training and the preventive efficacy of exercise hours before every chemotherapy cycle.

While the role of exercise therapy to improve chemotherapy-induced cardiovascular outcomes has been promising in animal models, large-scale randomized control trials are needed to evaluate its effectiveness in preventing anthracycline-induced cardiomyopathy in cancer patients (56-59).

Summary and perspectives

Chemotherapy-induced cardiotoxicity include a combination of mechanisms which influence several intracellular signaling cascades, critical to both cancer progression and the normal functioning of the heart. Larger future studies are necessary to reach a point of secure cytostatic therapy, improved patient survival and quality of life. Until that moment, baseline and serial cardiac evaluation is recommended to facilitate early identification and treatment of cardiotoxicity.

Conflict of interests

None.

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