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CARDIOTOXICITY IN ONCOLOGY: PREVENTION AND MANAGEMENT THROUGH CARDIOVASCULAR REHABILITATION

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Abstract

With advancements in screening, diagnosis, and treatment, cancer-related mortality is declining, and life expectancy for cancer patients is increasing by up to 30%. However, these patients often face increased cardiovascular risks due to hypertension, metabolic syndrome, and type 2 diabetes, as well as the cardiotoxic effects of cancer therapies. Chemotherapy drugs like anthracyclines, trastuzumab, and 5-fluorouracil can hurt the heart through oxidative stress, apoptosis, and mitochondrial dysfunction. This can cause heart failure, coronary heart disease, and arrhythmias, among other problems. Cardiovascular rehabilitation (CR) has emerged as a key strategy to mitigate these effects. Studies involving breast cancer patients and other cancer populations have demonstrated that CR programs, involving high-intensity interval training and moderate-intensity exercises, improve cardiorespiratory fitness and reduce cardiovascular risks in cancer patients. Despite challenges such as patient reluctance due to distance from specialized centers, telerehabilitation has proven to be a viable alternative. CR not only improves peak VO2 but also reduces systemic inflammation and promotes muscle mass gain while lowering mortality and healthcare costs associated with post-cancer therapy complications. Multidisciplinary involvement—integrating cardiologists, oncologists, psychologists, and nutritionists—enhances outcomes, improving both cardiac fitness and quality of life for cancer patients. Further research highlights the need for early intervention and customized CR programs to minimize cardiovascular toxicity and optimize patient recovery post-chemotherapy.

Keywords: *cardiac rehabilitation, cardiotoxicity, oncology, heart failure, chemotherapy.*

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Rezumat

Datorită progreselor în materie de screening, diagnostic și tratament, mortalitatea cauzată de cancer este în scădere, iar speranța de viață a pacienților cu cancer a crescut cu până la 30%. Cu toate acestea, acești pacienți se confruntă adesea cu riscuri cardiovasculare crescute din cauza hipertensiunii arteriale, a sindromului metabolic și a diabetului de tip 2, precum și a efectelor cardiotoxice ale terapiilor oncologice. Chimioterapeuticele, precum antraciclinele, trastuzumab și 5-fluorouracilul, pot afecta cordul prin creșterea stresului oxidativ, apoptoză și disfuncție mitocondrială. Aceste mecanisme pot duce la apariția insuficienței cardiace, boli coronariene și aritmii. Reabilitarea cardiovasculară (RC) a apărut ca o strategie-cheie de atenuare a acestor efecte. Studiile care au implicat pacienți cu cancer mamar sau alte tipuri cancer au demonstrat că programele de RC, care implică antrenamente ce cuprind exerciții de intensitate ridicată și exerciții de intensitate moderată, îmbunătățesc capacitatea cardiorespiratorie și reduc riscurile cardiovasculare. Telereabilitarea s-a dovedit a fi o alternativă viabilă când vine vorba de pacienții care evită participarea la astfel de programe din cauza distanței față centrul specializat. CR nu numai că îmbunătățește VO_2 de vârf, dar reduce, de asemenea, inflamația sistemică și promovează creșterea masei musculare, reducând în același timp mortalitatea și costurile asistenței medicale asociate complicațiilor terapiei post-cancer. Implicarea multidisciplinară - integrarea cardiologilor, oncologilor, psihologilor și nutriționiștilor - sporește rezultatele, îmbunătățind atât condiția fizică cardiacă, cât și calitatea vieții pentru pacienții cu cancer.

Cuvinte cheie: *recuperare cardiacă, cardiotoxicitate, oncologie, insuficiență cardiacă, chimioterapie.*

Introduction

With the development of screening, diagnosis, and treatment methods, cancer death rates are falling. Estimates show that in the coming years, life expectancy among people diagnosed with cancer will increase by up to 30%[1].

Even though cancer-related mortality is decreasing, patients are predisposed to an increased cardiovascular risk, often being diagnosed with hypertension, metabolic syndrome, and type 2 diabetes mellitus, in addition to the negative effects of cancer treatment and the disease itself[2]. Patients with cancer have lower cardiorespiratory fitness than the general population. This may be due to several factors, including a lack of physical activity. Secondly, increased cell destruction and systemic inflammation lead to damage to several organs, including the heart[3]. Many of the chemotherapies have cardiotoxic effects with an impact not only on the heart muscle but also on the functional endothelium[3,4].

The most common post-chemotherapy cardiovascular complications are heart failure, coronary artery disease, valvular valve disease, arrhythmias, hypertension, thromboembolism, peripheral vascular damage, and even stroke. Pulmonary hypertension and pericardial damage can also accompany these complications[5].

For these patients, more and more studies emphasize the importance of cardiovascular recovery. A well-designed recovery program, based on a multidisciplinary team, could improve both cardiorespiratory fitness and quality of life in cancer patients. Despite the potential benefits of such a program on quality of life, it is crucial to conduct a comprehensive assessment of patients before initiating the program to precisely identify the types of exercises they can perform, thereby preventing further complications[6].

Search Strategy

For this literature review, we used searching terms the association between the following words: "cardiac rehabilitation," "cardiotoxicity," and "chemotherapy." We utilized PubMed and Google Scholar as our search platforms. We included in this review only studies written in English, involving participants over the age of 18 years, that focused on cardiovascular recovery in patients who experienced cardiac damage as an adverse reaction after chemotherapy.

Cardiotoxic Effects of Oncologic Therapy

In recent years, more and more studies have reported the negative effects of cancer and cancer treatment on the cardiovascular system. However, there are a few studies that question whether cardiovascular disease could be a precursor to some cancers[7,8,9].

To determine cardiovascular risk, echocardiography evaluates patients for global longitudinal strain, left ventricular ejection fraction, and valvular heart disease[10].

Anthracyclines, one of the most often used medication classes, present a 9% risk of cardiotoxicity. Among the mechanisms implicated are the effects on autophagy in cardiomyocytes, the peroxidation of cell membrane lipids, which leads to cardiomyocyte death, and the inhibition of mitochondrial biogenesis[11]. Trastuzumab affects apoptotic processes and induces mitochondrial energetic diffusion by disrupting ErbB4/ErbB2 heterodimerization[12,13]. By several mechanisms, 5-fluorouracil administration can lead to coronary vasospasm and even direct myocardial damage. Furthermore, this drug has an impact on

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apoptotic processes and mitochondrial function. Cisplatin and tyrosine kinase inhibitors also have effects on mitochondrial DNA. In addition, cardiac injury caused by these two classes of drugs is mediated by oxidative stress and apoptosis[5].

Chemotherapy essentially leads to cardiac cardiotoxicity through its negative impact on DNA, apoptosis, mitochondrial and endothelial function, and increased oxidative stress. Exercise can mitigate the negative impact of cancer therapy. Sport not only decreases oxidative stress but also prevents telomere shortening, preserves vascular function, and decreases cardiovascular risk[14,15].

Cardiac Rehabilitation

In 2022, the results of a randomized clinical trial involving 29 patients diagnosed with breast cancer are published. The study distributed 14 patients into the control group and 15 patients into the cardiovascular recovery program group. In the end, only 11 participants from each group completed the program. Before their inclusion in the program, the participants underwent an echocardiographic assessment and a cardiopulmonary test. For 10 weeks, they participated in 30 visits that included exercise on a treadmill, cycle ergometer, or elliptical trainer at intervals of 4 minutes of high-intensity exercise (HIIT) alternating with 3 minutes of moderate-intensity exercise. Patients received instructions to perform 5 minutes of warm-up and recovery at the beginning and end of the exercises, respectively. Participants in the exercised group showed an improvement in cardiac fitness and an increase in VO_2 peak, in contrast to the control group, which demonstrated a slight decline. However, we observed no significant improvements in global longitudinal strain or troponin values[10].

The goal of a 2023 study, which included 191 cancer patients, was to evaluate the advantages of cardiovascular recovery in patients receiving oncologic treatment. Of all patients included in the study, 37% had undergone cardiotoxic treatment. Prostate cancer accounted for 18% of the patients, skin cancer for 12%, colon cancer for 9%, and breast cancer for 8%. Most of them were female, ex-smokers with low exercise capacity. At the end of the study, there was an improvement of about 1 METS among cancer patients ($p < 0.001$) and a decrease in abdominal circumference. The study concluded that cardiovascular rehabilitation programs improve patients' health status and quality of life and that routine inclusion of patients in such programming would lead to a decrease in mortality and much lower expenditures, considering the frequency of cardiovascular complications post-cancer therapy[16].

In 2024, a study was published that aimed to investigate the effectiveness of cardiovascular recovery in patients undergoing treatment with a possible cardiotoxic effect. The study included 122 patients with breast cancer diagnoses receiving treatment with anthracyclines and/or anti-HER2 antibodies. Half of the patients were assigned to the intervention group and half to the control group.

A cardiovascular specialist continuously monitored the participants in the cardiovascular rehabilitation program. The control group received telephone instructions on the type of exercises to perform only once every two months. Regardless of their assigned group, patients did not exhibit a significant decrease in ejection fraction, a common occurrence in patients on oncologic-targeted medication, at the end of the study. In addition, patients in the intervention group showed a significant weight loss among obese individuals. It appears that a well-designed cardiovascular rehabilitation program can significantly attenuate the decline in left ventricular ejection fraction in these patients and thereby decrease the cardiac toxic impact[17].

A cardiovascular rehabilitation program for the prevention of cardiovascular toxicity included 262 patients for 3 months between January 2014 and January 2022, but only 205 patients were able to complete the study. All those included were first assessed by a cardio-pulmonary exercise test performed on a cycle ergometer and were electrocardiographically monitored throughout the assessment. Furthermore, patients were questioned about their quality of life and fatigue status, as well as the type of therapy they were receiving. Throughout the program, patients had the option to participate in both hospital-based and hybrid home and hospital-based training. 71.3% of the patients showed an increase in peak VO_2 from 23.1 ml/kg/min to 25.6 ml/kg/min at the end of the program. Furthermore, a correlation was observed between the time when patients are involved in a cardiovascular recovery program and the negative impact of oncological medication. It appeared that exercise performed after anthracycline therapy would increase cardiac fitness, whereas in other oncologic therapies, the positive effect of recovery was seen both during and after therapy[3].

Cancer patients often experience a reduction in muscle mass, not only from prolonged rest but also from the disease itself. Sport not only prevents a decrease in peak VO_2 but also promotes an increase in muscle mass and a decrease in adipose tissue[18]. Moreover, physical activity leads to a decrease in systemic inflammation, further protecting against the proinflammatory effects of oncologic therapy[19]. For example, in a study in rats, it was observed that sport can reverse the cardiotoxic effect of doxorubicin[20].

Patients participating in the cardiovascular rehabilitation program require more than merely executing a series of well-designed training programs. Educating patients on enhancing their psycho-emotional well-being, nutrition, and lifestyle is crucial. Patients need to understand the additional risks linked to alcohol consumption, smoking, and a poor diet[21].

Often patients refuse to join such rehabilitation programs because of the distance to a specialized center. For these patients, telerehabilitation could be a viable option, as technological advancements have led to an increasing number of devices that can track the patient's heart rate, blood pressure, and

blood glucose in real-time [6]. Before entering such a program, patients must undergo physical, psycho-emotional, and nutritional evaluations to establish a well-developed program.

They will then receive remote monitoring throughout the following period(6,22). In 2019, a study was published in which 68 breast cancer patients were included. The study assigned half of the patients to the control group and the other half to the intervention group. The study aimed to investigate the effectiveness of an online cardiovascular recovery program to prevent the adverse effects of chemotherapy. This program was carried out over an 8-week period and included 5 strength exercises performed for 15-30 minutes, tailored to the patient.

At the end of the experiment, it was observed that the walking distance on the 6-minute test increased in the patients in the recovery group (from an average of 421.38 m to 483.46 m), while it decreased in the control group (from an average of 480.13 m to 453.79 m). Furthermore, the inclusion of patients in the recovery program led to an improvement in their physical condition, a crucial factor for this group of patients, as a healthy physical state can positively influence their chemotherapy response[23].

Conclusions

As therapies for patients with oncologic pathology evolve, it is desirable to increase the focus on pharmacologic and non-pharmacologic methods to prevent the negative effects of these drugs. Cardiovascular recovery should not only be based on physical exercise but also on educating patients about additional cardiovascular risk factors. The cardiologist can watch for possible cardiovascular complications and adjust the intensity of exercise to minimize potential risks to the patient.

The oncologist, on the other hand, monitors the patient's health status, such as the risk of infection, medication complications, or possible disease-related complications. The involvement of a team consisting of an oncologist, cardiologist, psychologist, nutritionist, and physiotherapist in the recovery process can lead to a decrease in the cardiac toxicity of the medication but also to improved cardiac fitness and quality of life in cancer patients.

Additionally, telerehabilitation offers a promising solution for patients unable to access specialized centers, expanding the accessibility and effectiveness of these programs. Ongoing research and patient education are crucial for optimizing cardiovascular recovery and minimizing risks.

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