Viewpoint

Functional Capacity in Cardiotoxicity: Effects of Physical Exercise

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Abstract

Heart failure induced by chemotherapy is an adverse event of cancer treatment that results in high morbidity and mortality. Previous studies have shown that physical exercise improves functional capacity in patients with heart failure due to other etiologies. However, studies with a multimodal approach, including exercise interventions in patients with cardiotoxicity, are still scarce in the literature. The objective of this article was to discuss the effects of physical training in patients with heart failure induced by chemotherapy and the role of cardio-oncological rehabilitation as a tool to improve functional capacity and quality of life in this group of patients.

Introduction

The evolution that oncology has achieved in recent decades, both in diagnostic methods and therapeutic efficacy, has resulted in more cancer survivors. This has brought the later costs of successful oncological therapy to the surface, for example, treatment-induced cardiovascular toxicity. This situation is defined by early or late damage to the cardiovascular system, which originated during or after cancer treatment, as a result of antineoplastic therapies.[1] Although it does not occur in the majority of survivors, cardiotoxicity is the main cause of death associated with oncological treatment, especially in breast cancer survivors.[2] The complexity of cancer care and the management of multiple comorbidities presented by patients demonstrate that it is necessary for them to receive an integrated and multidisciplinary therapeutic approach.[3]

Cardiotoxicity can be caused both by classical chemotherapy treatment and by more modern strategies with radiotherapy, leading to various cardiovascular effects, such as arrhythmias, cardiomyopathy, endothelial dysfunction, and heart failure.[4] Different definitions have been proposed for cardiac dysfunction associated with cancer therapy. The most recent include, in addition to the severity of symptoms or altered echocardiographic parameters, such as reduced ventricular function, changes in global longitudinal strain or cardiac biomarkers.[5]

Keywords

Exercise; Cardiotoxicity; Cardiac Rehabilitation

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Chemotherapy agents such as anthracyclines have been significantly associated with an increase in the incidence of cardiotoxicity and its severe consequences, such as heart failure and cardiomyopathy.[6,7] Risk increases significantly depending on the dose used or the association with other drugs, such as trastuzumab.[8,9]

There effects are often clinically silent until their severity causes symptoms and requires treatment; the timeframe can range from days to years after chemotherapy. For anthracyclines alone, the negative effects on cardiac function can appear up to 20 years after treatment, whereas, in combination with trastuzumab, cardiac complications are earlier, and they may be present up to 2 months after their use, in 27% of patients.[10] A study of leukemia survivors treated with anthracyclines showed worsened left ventricular shortening fraction and contractility 12 years after diagnosis.[11]

Pharmacological and non-pharmacological strategies, such as ceasing smoking and alcoholism, control of cardiovascular risk factors, healthy diet, weight maintenance, and encouragement of aerobic physical exercise practice, have increasingly proven to be effective as cardioprotective measures.[12] Studies have shown that physical exercise is an effective tool to mitigate the effects of chemotherapy on the cardiovascular system.[13,14]

Early diagnosis and intervention can prevent progression to heart failure in patients with cardiotoxicity.

Although there is substantial evidence of the benefits of physical exercise before and during therapy with cardiotoxic drugs, there is a lack of studies that demonstrate the impact of exercise in adult patients with chemotherapy-related heart failure, and it is not clear whether these interventions can be performed with the same effectiveness as in other populations.

In this article, we seek to address the impact of physical training on patients with heart failure induced by chemotherapy and the role of cardio-oncological rehabilitation as a tool for improving functional capacity in this group of patients.

Impact of cardiotoxicity on functional capacity

The reduction in cardiorespiratory fitness in patients with cancer is multifactorial. The patients are usually less active, and they commonly have other complications secondary to the disease, such as pulmonary and musculoskeletal alterations. It is also necessary to consider that patients with cancer are generally older and are subject to the deleterious effects of aging itself. Reduced functional capacity can also be a consequence of the treatment itself.

Cancer patients show a reduction between 5% and 22% in physical capacity, regardless of the antineoplastic regimen used, even in the absence of cardiotoxicity.[15] A study that involved 248 women with breast cancer between 40 and

50 years of age, divided according to the treatment phase or presence of metastasis, showed an average reduction of 32% in functional capacity compared to healthy controls.[16]

A study on patients with esophageal cancer showed a significant reduction in cardiac function and physical capacity immediately after the end of chemoradiotherapy.[17]

Cumulative doses of anthracyclines also appear to impact exercise capacity, even in the absence of systolic dysfunction, as shown by a study of childhood cancer survivors.[18]

Effects of physical training

The result of a meta-analysis of 27 studies published by Scott et al. showed that physical training is an effective strategy to improve physical capacity in patients with early-stage cancer, in addition to being safe and feasible.[19]

Fatigue associated with cancer is a complaint frequently reported by patients, and evidence suggests that physical training promotes a significant reduction in symptoms.[20]

In a study published by Courneya et al., aerobic and resistance physical training significantly improved physical fitness, body composition, and chemotherapy completion rates in patients with breast cancer.[21] Other studies have shown that exercise also improves functional capacity, quality of life,[22,23] and possibly the survival of patients with cancer.[24]

In heart failure, it is known that functional capacity is markedly reduced, and studies have shown an improvement of 12% to 31% with physical training.[25]

Some randomized clinical trials have demonstrated potential improvement in cardiovascular health in non-oncology patients with heart failure through exercise rehabilitation,[26-28] and meta-analyses have shown positive effects on cardiac function and quality of life.[29-33]

The effects of exercise in patients undergoing chemotherapy have mainly been studied in terms of its cardioprotective role. In an observational study, Foulkes et al. investigated the role of exercise or usual care in the functional capacity and echocardiographic parameters of 28 women with breast cancer undergoing chemotherapy with anthracyclines, after 4 and 16 months of treatment. After 4 months of treatment, the group undergoing training showed a 6% reduction in peak oxygen consumption (VO_2) compared to the usual care, where this reduction was 18%. This reduction was maintained over 16 months. Despite small reductions observed in resting left ventricular ejection fraction, only 2 patients met the criteria for defining cardiotoxicity.[34] The mean reduction of 8% in physical capacity over the 16 months becomes even more relevant when we consider that the aging is typically associated with a reduction of 8% to 23% per decade.[35]

A single randomized study evaluated the impact of physical exercise on functional capacity in patients with chemotherapy-related cardiomyopathy. Participants were randomized to a control group or a group that received supervised training for 16 weeks. However, 78% of the patients selected for the supervised group did not accept to participate in the original design and received home training as an alternative. The exercise program consisted of 30 minutes of supervised exercise on a stationary bicycle, at an intensity of 50% of heart rate reserve, at a training frequency of 3 times/week for 16 weeks. The home program began with a supervised session, followed by prescription for maintenance of aerobic exercises such as walking, in addition to counting steps using a pedometer, for 16 weeks. Intensity was assessed using the Borg "6–20" rating of perceived exertion (RPE) scale at an RPE of 12. Outcomes included evaluation of functional capacity by peak VO_2, left ventricular ejection fraction, severity of heart failure symptoms using the MD Anderson Symptom Inventory for heart failure (MDASI-HF), quality of life using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), and physical activity level in hours of exercise and intensity. Of the 16 participants randomized for training, only 10 completed the study, and 8 underwent functional capacity assessment by ergospirometry. At the end of the study, there was a significant improvement in quality of life and potential improvement in functional capacity assessed by peak VO_2 in the group that underwent training ($p < 0.05$). There were no statistically significant differences in left ventricular ejection fraction, symptom scores (MDASI-HF), or physical activity level. The sample size and the difficulty in randomization to a supervised program constituted important limitations of this study.[36]

In a retrospective study of 90 patients with cancer who had heart failure, 12 weeks of aerobic training did not result in an improvement in peak VO_2 or quality of life compared to the control group; however, the etiology of heart failure was categorized as ischemic or non-ischemic, and data such as type of cancer, disease stage, or antineoplastic therapy used were not collected.[37]

Future perspectives

Cardiotoxicity is one of the adverse effects of treatment that most compromises functional capacity and quality of life, with an impact on mortality, regardless of oncological prognosis.[38] However, there is a shortage of studies involving this patient population in the setting of cardiac rehabilitation.

Cardiac rehabilitation consists of a multidisciplinary program, based on physical exercise, with nutritional and psychological counseling.[39] It is highly recommended in patients with coronary artery disease and heart failure[40] owing to its numerous benefits, not only in improving physical capacity and quality of life, but also in reducing all-cause mortality and hospitalizations.[41] Based on this knowledge, the development of a more comprehensive model has been proposed to involve patients with cancer and high risk for developing cardiovascular diseases, in addition to patients with cardiotoxicity related to cancer therapies, using a multimodal approach, in a model known as Cardio-Oncology Rehabilitation (CORE).[42]

The incorporation of this rehabilitation model into traditional programs, however, requires knowledge of the specificities of each type of cancer. Exercise programs must also respect the individual characteristics of patients, such as functionality, disease stages, the presence of metastases, or contraindications.

Some cardiac rehabilitation centers have adapted to receive patients in the context of cardio-oncological rehabilitation,

including other professionals in their multidisciplinary teams and offering support in different phases of treatment.

One aspect that must be considered is that the few available cardiac rehabilitation services are still underused. It is estimated that only 20% to 30% of patients with an indication for cardiac rehabilitation are referred to a rehabilitation center.[43] Low adherence to supervised programs is another evident problem, associated with limited access due to distance from rehabilitation centers, costs, difficulty reconciling working hours, socioeconomic level, and frequent limitations due to the presence of other cancer-related symptoms. This is reflected in the difficulty in conducting studies and their results.

Conclusion

Undoubtedly, as with cardiovascular disease, physical exercise brings many benefits to patients with cancer at different disease stages or treatment phases. However, there is still a shortage of studies evaluating the therapeutic use of physical exercise in patients who develop heart failure as a consequence of treatment.

The use of structured physical exercise as an adjuvant therapy for manifest cardiotoxicity, nonetheless, appears to be indicatable and potentially beneficial.

Incorporating new models of cardiac rehabilitation into traditional programs, including patients at high risk for development or patients who already have manifest cardiotoxicity, and conducting more studies involving these patients are fundamental strategies for producing more robust evidence.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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