Review Article

Cardiovascular Rehabilitation in Patients with Cancer

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Abstract

Advances in cancer treatment have increased patient survival, as well as susceptibility to cardiovascular disease, not only due to the increase in risk factors but also as a result of the treatment itself.

Cardiotoxicity related to antineoplastic drugs is one of the most feared cardiovascular effects during or after chemotherapy treatment, and it is associated with unfavorable prognosis in cancer survivors. Moreover, it reduces physical capacity and quality of life. In this scenario, the multimodal model of cardio-oncological rehabilitation has become a fundamental strategy in patients with high cardiovascular risk or risk for the development of cardiotoxicity, as well as for those with already established heart disease.

In this article, we will address the role of cardiac rehabilitation in patients with cancer and its particularities.

Introduction

Early detection and assertive treatment have transformed cancer from a practically fatal disease to, in many cases, a chronic condition. Due to the progress in oncological treatment and increased survival, the time of exposure to cardiovascular risk factors has become longer, and with it the prevalence of cardiovascular diseases in patients with cancer has increased.[1]

Successful oncological treatment, in many cases, is only possible with the use of drugs with a high potential for cardiotoxicity.[2] Thus, in several types of cancer, it is not uncommon for the risk of cardiovascular death to exceed the risk of tumor recurrence.[3] In this context, Patnaik et al. reported that cardiovascular disease was the leading cause of death in elderly female breast cancer survivors without previously diagnosed cardiovascular disease.[4] In relation to incidence, the occurrence of cardiotoxicity varies between 5% and 30% in clinical series, and it is more frequent in a subgroup with the following known risk factors: extremes of age, previous ventricular dysfunction, arterial hypertension, diabetes, use of combined chemotherapy, and mediastinal radiotherapy.[5]

Considering that most cancers can currently be considered as chronic diseases and that physical training is known to be beneficial in the treatment of several cardiovascular diseases, during the last two decades, several researchers have focused on the subject of physical activity and cancer. These studies have culminated in the recommendation of physical training not only for prevention, but also as an adjuvant therapy for diagnosis of different types of cancer.[6-8] The objective of this article is to present cardio-oncology rehabilitation in the current context.

Pre-participation assessment

The initial cardiological assessment of patients undergoing cancer treatment who will be submitted to potentially cardiotoxic therapies should include careful anamnesis and physical examination, a 12-lead resting electrocardiogram, and assessment of left ventricular function by echocardiography.[7]

It is important to monitor signs and symptoms of heart failure (HF) during chemotherapy treatment, because, although it occurs rarely, early clinical manifestations of toxicity from oncological treatment can culminate in cases of fulminant acute myocarditis and/or severe arrhythmias. As toxicity can appear at any time after the use of chemotherapy drugs (up to several years after the end of treatment), constant surveillance of clinical manifestations of HF is fundamental, especially during the first year after chemotherapy.

Table 1 contains important information to take into account before starting physical activity in patients with cancer, such as clinical assessment, with the suggestion of performing pre-participation stress tests, assessment of peculiarities of the consequences of cancer treatment (absence of significant anemia or thrombocytopenia, absence of neutropenia), and factors intrinsic to cancer treatment (well-being, absence of nausea/vomiting, absence of active infections or metabolic diseases).

Keywords

Rehabilitation; Cancer; Physical activity.

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Table 1 – Complementary assessment of patients with cancer before participation in rehabilitation. Adapted from Gilchrist et al.[8]

Normal functional testing
Cardiopulmonary exercise testing
Resting blood pressure ≤160/90 mm Hg
Normal blood pressure response to exercise
Absence of ischemia
Absence of ventricular arrhythmias
Normal O_2 saturation
Absence of symptoms
6-minute walk test
Resting blood pressure ≤160/90 mm Hg
Laboratory tests
Absence of severe anemia (< 8.0 g/dL)
Absence of neutrophilia > 500 mm^3
Platelet count > 50,000/μL
Absence of symptoms
Nausea during exercise
Vomiting within the past 24 hours
Disorientation
Blurred vision
Complications associated with cancer
Acute infection
Acute metabolic disease
New lymphedema
Mental or physical alteration during exercise
Unhealed wound
Bone or brain metastasis
Self-monitoring skills
Understands exercise functions
Understands how to use the equipment

Roles of functional capacity and physical activity

Functional capacity is a strong predictor of mortality and cardiovascular events,[9] and it is used both for prognosis and for indicating therapeutic intervention in a broad range of cardiovascular and non-cardiovascular diseases. Observational studies have reported a reduction in the number of cardiovascular events in people who regularly perform aerobic physical activity.[10]

Patients with cancer have markedly reduced physical capacity in the early stages of the disease. A study carried out with women with breast cancer between 40 and 50 years of age showed an average reduction of 32% in physical capacity in relation to healthy controls, at different phases of treatment. The same study also showed that peak oxygen consumption (VO_2) can be an independent predictor of survival in metastatic disease.[11]

There is evidence that cancer treatment also has a negative effect on physical capacity, regardless of the presence of cardiotoxicity. A meta-analysis of 27 studies including women with breast cancer showed a 17% and 25% reduction in physical capacity before and after adjuvant therapy, respectively.[12]

One of the most concerning adverse effects of antineoplastic therapy is undoubtedly cardiotoxicity. The presence of systolic ventricular dysfunction results in a significant increase in mortality, in addition to worsening of quality of life.[13] In addition to cardiovascular changes, adjuvant treatment compromises other systems such as skeletal muscle, resulting in loss of lean mass and muscle function with a consequent impact on functional capacity.[14]

A retrospective study of childhood cancer survivors showed a positive correlation between increased anthracycline dose and reduced physical capacity. In that same study, in spite of higher levels of NT-proBNP, only diastolic dysfunction was found as a structural alteration.[15]

Radiotherapy and/or chemotherapy are associated with reduced physical capacity in patients with cancer. Figure 1 shows the main determinants of low physical capacity in patients with cancer.

It is known that exertion intolerance is one of the most striking characteristics of HF, and it is associated with worse physical capacity, quality of life, and prognosis.[16] Studies have already shown that reduced physical capacity in patients with HF occurs similarly in different etiologies, such as ischemic, idiopathic, or hypertensive;[17] however, studies in humans who have developed HF secondary to cancer treatment are still scarce in the literature.

Benefits of physical activity in patients with cancer

In patients with HF, controlled studies have also demonstrated a positive impact of physical activity as an additional therapeutic measure, with improved exertion tolerance.[18] A study published by Antunes-Correa et al., showed that the improvement in physical capacity after 4 months of physical training occurs in a similar manner in patients with HF, regardless of etiology. However, this study did not include patients with cardiotoxicity.[17]

In experimental studies, there is a suggestion that exercise before the use of anthracyclines or aerobic training before and during the infusion of anthracyclines could reduce the impact of cardiotoxicity. Hayward et al.[19] used a juvenile rat model to assess whether a training protocol would reduce the impact of anthracycline-induced cardiotoxicity. One group underwent aerobic training concomitantly with doxorubicin infusion, and the study concluded that aerobic training, concomitant with the beginning of doxorubicin infusion, reduced doxorubicin-induced cardiotoxicity, in comparison with the untrained rats. Another study by Parry et al. demonstrated that the therapeutic efficacy of doxorubicin was not affected in rats trained prior to treatment with anthracyclines, but there was a reduction in ventricular dysfunction in the group of trained rats.[20,21] Several other

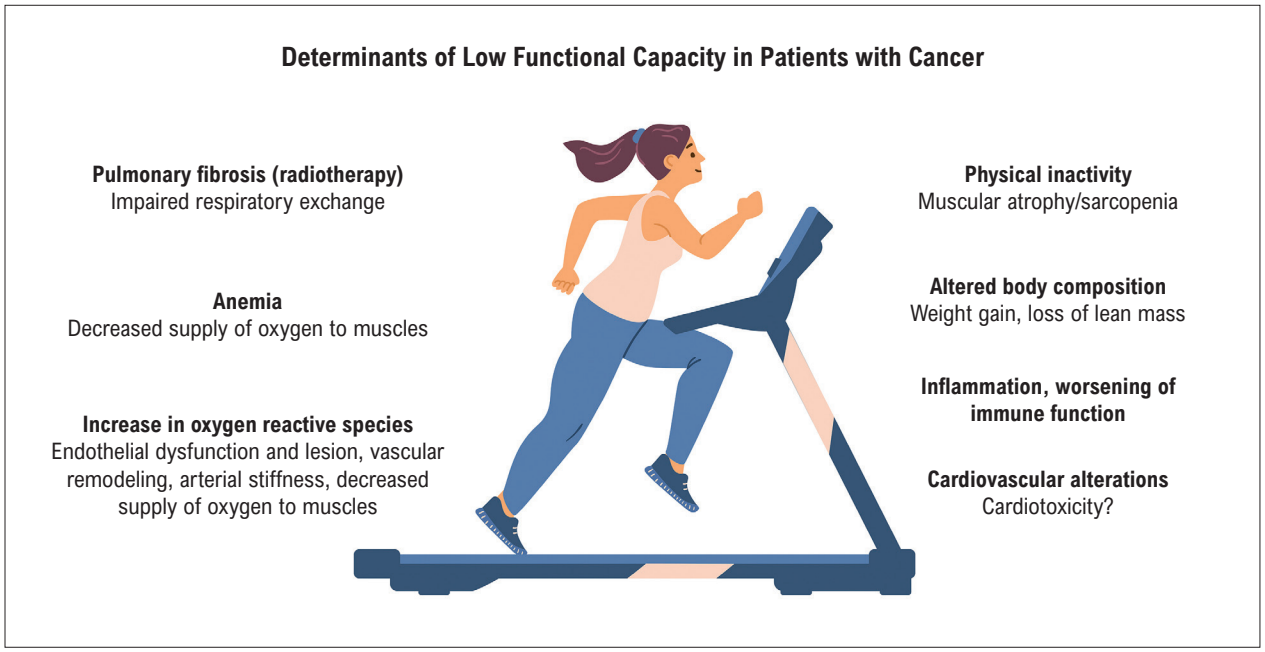

Figure 1 – *Determinants of Low Functional Capacity in Patients with Cancer.*

studies have also suggested a protective role for exercise both in acute toxicity of doxorubicin[22,23] and reducing the incidence of HF and ventricular dysfunction.[19,24,25]

In patients with cancer, several small randomized studies have demonstrated positive effects of exercise, such as an increased peak VO_2, improved vascular function, and improved LVEF (Figure 2).[8] Another, more robust study, with 4015 patients followed for 8 years, documented a reduced risk of events proportional to the performance of physical activity before the diagnosis of cancer; event-free survival was higher in patients who had previously practiced physical activity.[26] There is also a meta-analysis of more than 70,000 patients with cancer that demonstrated a strong association between functional capacity and prognosis, with a reduction in mortality in patients with better functional capacity over a 16-year follow-up.[27]

An important aspect of patients with cancer is that, in many cases, they face attacks by various agents, whether related to cardiovascular risk factors already present even before the diagnosis of cancer, the direct injury induced by cancer treatment, or indirect consequences of treatment such as sedentary lifestyle, weight gain, loss of muscle mass, among others.[28] Accordingly, exercise emerges as a therapeutic proposal to attenuate these multiple "hit points", given that it controls cardiovascular risk factors, improving the functional capacity of patients, reducing fatigue and improving quality of life.[28]

Components of rehabilitation in patients with cancer

The benefits of cardiovascular rehabilitation programs for non-oncological patients with cardiovascular comorbidities, such as coronary disease and HF are well established and are included as class I, level of evidence A recommendations, in all cardiology guidelines.

There is, thus, a considerable similarity in the assessment of patients with cancer in relation to the components and recommendations of prescription of physical activity. In both situations (cardiovascular and oncological rehabilitation), a multidisciplinary team is recommended, with prescription of aerobic physical activity and strength (resistance) exercises, in addition to education regarding the disease, treatment, psychosocial assessment, and lifestyle interventions, to optimize the control of cardiovascular risk factors (such as high blood pressure, diabetes, dyslipidemia, obesity, and smoking).[29] These components can be offered in rehabilitation centers with greater multidisciplinary supervision or as exercises performed outside the rehabilitation center, and it is highly recommended to individualize the prescription of physical activity and periodic reassessments to adjust the stimulus.[29] Figure 3 shows practical suggestions for implementing strategies for rehabilitation services and possible applications for monitoring patients who perform activities outside the rehabilitation center.[8]

However, in spite of similarities in these components, there are several particularities in advising patients with cancer. An example of this limitation regards the adverse effects of chemotherapy, and patients may experience fatigue, nausea, indisposition, loss of muscle mass, or postoperative convalescence, which are factors that do not correspond to the routine of cardiology patients.[30]

Table 2 contains data that summarize this comparison between cardiovascular rehabilitation and cardio-oncological rehabilitation, with several particularities related to patients with cancer.[6]

Regarding the objective prescription of intensity, frequency, and duration of aerobic and resistance exercises, there is no specific formal recommendation for patients

Setting	Clinical Outcomes	Cardiovascular Outcomes
Adjuvant		
Breast	↓ CVD Events ↓ CAD Mortality	↑ ↔ ↓ CRF ↓ LVEF
Prostate		↑ CRF
Colorectal		↑ CRF
Mixed (Meta-analysis)		↑ CRF
Post-adjuvant		
Breast	↓ CVD events ↓ All-cause mortality	↔ ↑ CRF ↑ Vascular function
Prostate		↑ CRF ↑ Vascular function ↔ Lipide profile ↔ Blood pressure
ASCC	↓ CVD events ↓ All-cause mortality	
Testicular		↑ CRF ↑ Vascular function ↑ Framingham risk score
Colorectal	↓ All-cause mortality	↑ ↔ CRF
Leukemia		↑ CRF
Lymphoma		↑ CRF
Mixe (Meta-analysis)		↑ CRF

Figure 2 – *Oncological scenarios studied with physical activity and observed outcomes. Even though they were small, there are multiple studies with various outcomes such as improved functional capacity, reduced mortality, improved vascular function, and improved left ventricular ejection.[8] ASCC: adult survivors of childhood cancer; CAD: coronary artery disease; CRF: cardiorespiratory fitness; CVD: cardiovascular disease; LVEF: left ventricular ejection fraction.*

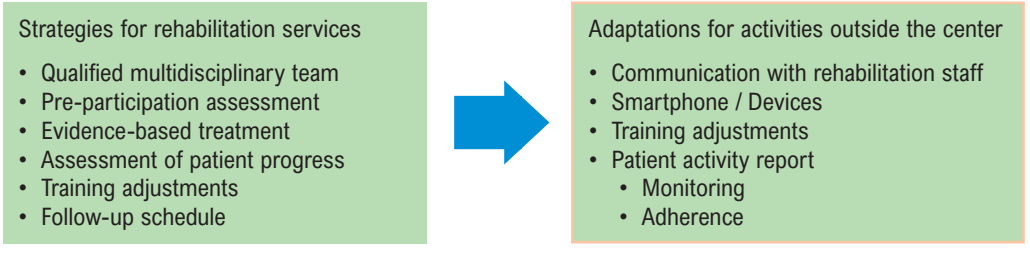

Figure 3 – *Strategies for rehabilitation services and solutions for monitoring patient adherence outside the rehabilitation center.[8]*

with cancer. Table 3 contains objective recommendations for exercise prescription based on guidelines for patients in cardiovascular rehabilitation, which may serve as parameters for prescription in this scenario.[29]

Conclusion

Rehabilitation is a multidisciplinary intervention with a great impact on improving functional capacity and quality of life and reducing cardiovascular outcomes. Patients with cancer, in addition to frequently having cardiovascular risk factors, undergo cancer therapy that can cause cardiotoxicity and culminate in a sedentary lifestyle with loss of muscle strength. Accordingly, with due attention to particularities in this patient profile, oncological rehabilitation should be encouraged and prescribed with the aim of complementing specific cancer therapy.

Author Contributions

Conception and design of the research: Schwartzmann PV, Gonzales A, Castro RRT; Acquisition of data:

Table 2 – Particularities of cardio-oncological rehabilitation in relation to cardiovascular rehabilitation. Adapted from Sase et al.[6]

Cardiac rehabilitation		Cardio-oncological rehabilitation
General conditions		Type of cancer, stage, metastasis
		Health conditions
		Treatment-associated cardiovascular alterations
		Lymphoma, ostomies, infection
		Blood count (cell count)
		Depression, fatigue, quality of life
		Functional capacity
Lifestyle modifications	Nutrition	Cancer-specific nutritional assessment
	Weight control	Body composition (gain or loss of fat mass)
	Blood pressure	Treatment of systemic arterial hypertension
	Lipid profile	Dyslipidemia control
	Diabetes mellitus	Glycemic control
	Smoking	Specific referral
	Psychosocial follow-up	Mental support
	Physical activity	Reduce sedentarism, increase physical activity
Prescription of physical exercise		Development of training guidelines, implementation of cardio-oncologic rehabilitation, strategies to improve outcomes in patients with cancer

Table 3 – Practical recommendations for prescribing aerobic and resistance exercises. Adapted from Bozkurt et al.[29]

	Aerobic exercise	Resistance exercise
Frequency	5 days/week, moderate intensity 3 days/week, high intensity	2 to 3 consecutive days/week
Intensity	Heart rate limit Vary intensity (interval)	Set load and repetitions. Goal of 8 to 10 exercises, 1 to 3 sets, 8 to 16 repetitions
Time	30 to 60 minutes, or less if high intensity	Varies according to capacity
Type	Any activity that raises heart rate, such as running, walking, cycling, or dancing	Resistance bands, dumbbells, machines, or own weight

Schwartzmann PV; Analysis and interpretation of the data and Writing of the manuscript: Schwartzmann PV, Gonzales A; Critical revision of the manuscript for important intellectual content: Gonzales A, Castro RRT.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

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