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Impacto da reabilitação física na fadiga de pacientes onco-hematológicos submetidos a tratamentos citotóxicos

Porto Alegre
2025

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Dedicatória

Sigo
dedicando toda minha trajetória
acadêmica a quem me ilumina e
guiou até aqui. Dedico este trabalho
à minha guerreira Adriana Berleze,
que colocou em prática tudo o que
buscamos evidenciar com esta
pesquisa.
.

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RESUMO

Esta tese teve como objetivo incrementar o conhecimento referente ao manejo da fadiga relacionada ao câncer em diferentes fases do tratamento citotóxico antineoplásico, por meio da implementação da reabilitação física.
Métodos artigo 1: Esta revisão sistemática, conduzida de acordo com as diretrizes PRISMA e registrada no PROSPERO, avaliou o efeito da fisioterapia na fadiga relacionada ao câncer (FRC) durante o tratamento antineoplásico com quimioterapia. Revisão sistemática com metanálise de ensaios clínicos randomizados publicados entre 2010 e 2021 (EMBASE, MEDLINE, PEDro; SciELO e LILACS). Foram incluídos nesta revisão estudos que avaliaram o efeito da fisioterapia supervisionada (FS) no manejo da FRC em adultos submetidos a tratamento antineoplásico, comparados a um grupo controle (GC) que abrangia o tratamento usual ou qualquer prática não controlada, como recomendações sobre exercícios e educação em saúde. **Resultados artigo 1:** Um total de 22 estudos foram incluídos na revisão sistemática e 21 na metanálise, totalizando 1.992 indivíduos (GC = 973 e FS = 1.019). Houve redução na fadiga geral [DMP = − 0,69; IC 95% (− 1,15, − 0,22) p < 0,01; I2 = 87%; NNT = 3], com maior peso atribuído ao exercício combinado (44%). A fadiga física também foi reduzida [SMD= − 0,76; IC 95% (− 1,13, − 0,39) p < 0,01; I2 = 90%; NNT = 2], com maior peso para o exercício de resistência (50%) e maior efeito com o exercício combinado [SMD= −1,90; IC 95% (−3,04,−0,76) p<0,01; I 2=96%]. Houve redução na fadiga geral com intensidade moderada (74%) [SMD= −0,89; IC 95% (−1,61,−0,17) p<0,02; I2=90%] e fadiga física [SMD= −1,00; IC 95% (−1,54,−0,46) p<0,01; I^2=92%], enquanto a alta intensidade reduziu apenas a fadiga geral [SMD= −0,35; IC 95% (−0,51,−0,20) p < 0,01; I^2 = 0%]. O número total de sessões e de sessões semanais demonstrou contribuir para a redução da fadiga relacionada ao câncer. **Métodos artigo 2:** Objetivou-se comparar o efeito de três modos de reabilitação física sobre a fadiga relacionada ao câncer (FRC) de pacientes hospitalizados para o transplante de células-tronco hematopoéticas (TCTH). Ensaio clínico randomizado com pacientes submetidos ao TCTH, alocados em grupo aeróbio (AE), resistido (RE) ou combinado (C) para a realização de reabilitação física durante a internação hospitalar. Foram 5 sessões semanais, conforme viabilidade clínica, 15-20 minutos por sessão com intensidade moderada de exercício físico. Os desfechos avaliados foram FRC e desempenho físico (Teste do senta e levanta de 30 segundos – TSL30 e força de preensão palmar), além da viabilidade clínica para realização da reabilitação, segurança e adesão. **Resultado artigo 2:** Total de 45 pacientes completaram as intervenções (AE=14; RE=15; C=16). A viabilidade clínica geral foi de 70% (AE=68%; RE=67%; C=72%) e a adesão foi de 87% (AE=83%; RE=86%; C=92%). Nenhum evento adverso relacionado ao exercício físico foi registrado. A FRC não apresentou diferença significativa (p=0,89) entre os diferentes tipos de intervenção e manteve baixa oscilação entre pré e pós-TCTH quando os diferentes grupos foram unificados em uma amostra. O desempenho físico também não apresentou resultados significativos, tanto no TSL30 (p=0,62) e na força de preensão palmar (p=0,84).

Palavras-chave: Fisioterapia; Fadiga; Exercício físico; Desempenho físico funcional

ABSTRACT

This doctoral dissertation aimed to increase knowledge regarding the management of cancer-related fatigue in different phases of cytotoxic antineoplastic treatment, through the implementation of physical rehabilitation. **Methods article 1:** This systematic review, conducted according to the PRISMA guidelines and registered in PROSPERO, evaluated the effect of physiotherapy on cancer-related fatigue (CRF) during antineoplastic chemotherapy treatment. Systematic review with meta-analysis of clinical trials published between 2010 and 2021 (EMBASE, MEDLINE, PEDro; SciELO and LILACS). Studies that evaluated the effect of supervised physiotherapy (SP) on the management of CRF in adults undergoing antineoplastic treatment, compared to a control group (CG) that included usual treatment or any uncontrolled practice, such as recommendations on exercise and health education, were included in this review. **Results from article 1:** A total of 22 studies were included in the systematic review and 21 in the meta-analysis, totaling 1,992 individuals (GC = 973 and FS = 1,019). There was a reduction in general fatigue [DMP = − 0.69; 95% CI (− 1.15, − 0.22) $p < 0.01$; I2 = 87%; NNT = 3], with greater weight attributed to combined exercise (44%). Physical fatigue was also reduced [SMD = − 0.76; 95% CI (− 1.13, − 0.39) $p < 0.01$; I2 = 90%; NNT = 2], with greater weight for resistance exercise (50%) and a greater effect with combined exercise [SMD = −1.90; [95% CI (-3.04, -0.76) $p<0.01$; I^2=96%]. There was a reduction in overall fatigue with moderate intensity (74%) [SMD= -0.89; 95% CI (-1.61, -0.17) $p<0.02$; I^2=90%] and physical fatigue [SMD= -1.00; 95% CI (-1.54, -0.46) $p<0.01$; I^2=92%], while high intensity only impairs overall fatigue [SMD= -0.35; 95% CI (-0.51, -0.20) $p < 0.01$; I^2 = 0%]. The total number of sessions and weekly sessions is planned to contribute to the reduction of cancer-related fatigue. **Methods of article 2:** The objective was to compare the effect of three modes of physical rehabilitation on cancer-related fatigue (CRF) in patients hospitalized for hematopoietic stem cell transplantation (HSCT). A randomized clinical trial was conducted with patients undergoing HSCT, allocated to an aerobic (AE), resistance (RE), or combined (C) group for physical rehabilitation during hospitalization. There were 5 weekly sessions, according to clinical criteria, 15-20 minutes per session with moderate intensity physical exercise. The studies evaluated were heart rate control (HRC) and physical performance (30-second sit-to-stand test – 30SST and handgrip strength), in addition to clinical prediction for rehabilitation, safety, and adherence. **Results of article 2:** A total of 45 patients completed the disciplines (AE=14; RE=15; C=16). Overall clinical prescription was 70% (AE=68%; RE=67%; C=72%) and adherence was 87% (AE=83%; RE=86%; C=92%). No adverse events related to physical exercise were recorded. Functional cardiac performance (FCR) did not show a significant difference (p=0.89) between the different types of intervention and maintained low oscillation between pre- and post-HSCT when the different groups were unified into a single sample. Physical performance also did not show significant results, both in the 30-minute TSL (p=0.62) and in handgrip strength (p=0.84).

Keywords: Physiotherapy; Fatigue; Physical exercise; Functional physical performance

Objetivos de desenvolvimento sustentável:

- Saúde e bem-estar

Assegurar vida saudável e promover bem-estar para as pessoas de todas as idades, independente das comorbidades associadas e tratamentos envolvidos.

Implementar protocolos de exercício físico com segurança que promova saúde e bem-estar para os pacientes oncológicos.

- Indústria, inovação e infraestrutura

Promover a inovação na área de reabilitação em oncohemtologia.

Fomentar o incremento da infraestrutura de centros de tratamento onhematológico e de reabilitação.

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LISTA DE ABREVIATURAS E SIGLAS

FS	Fisioterapia supervisionada
FRC	Fadiga relacionada ao câncer
TCTH	Transplante de células-tronco hematopoéticas
TSL30	Teste do senta e levanta de 30 segundos
GC	Grupo controle
AE	Aeróbio
C	Combinado
RE	Resistido
FC	Frequência cardíaca
UFCSPA	Universidade Federal de Ciências da Saúde de Porto Alegre
CEP	Comitê de Ética em Pesquisa
ISCMPA	Irmandade Santa Casa de Misericórdia de Porto Alegre
TCLE	Termo de Consentimento Livre e Esclarecido

SUMÁRIO

1 CONTEXTUALIZAÇÃO

1.1 REPERCUSSÕES DO TRATAMENTO CITOTÓXICO COM QUIMIOTERAPIA DE ALTA DOSE

O tratamento antineoplásico é composto por diferentes modalidades, entre elas cirurgia, radioterapia, hormonioterapia, mas principalmente pela quimioterapia. Há uma diversidade de doenças que se beneficiam da quimioterapia, porém a associação dos eventos adversos com as complicações da doença de base podem deteriorar a capacidade funcional dos pacientes oncológicos e consequentemente prejudicar a qualidade de vida (HENRY et al., 2008; BO Y, JIANSHENG W, 2017; INCA, 2019). Esses tipos de consequências são frequentemente subnotificados e desvalorizados, uma vez que o foco terapêutico objetiva a cura da doença. Por isso, é possível identificar durante esse processo perda importante de força muscular, queixas de dor, inapetência, redução da autonomia, funcionalidade e sinais de fadiga que não melhora com o repouso (PENEDO et al., 2020).

A quimioterapia trata de forma sistêmica o câncer, atingindo concomitantemente células tumorais e sadias, e por isso os efeitos colaterais são tão diversificados. Apesar de ser utilizada tanto para tumores sólidos quanto para doenças hematológicas, é nesta última que as repercussões sistêmicas se manifestam de forma mais intensa, devido aos sinais prévios da própria patologia. Os agentes quimioterápicos podem ser administrados de maneira contínua ou intervalada, variando conforme o esquema terapêutico (INCA, 1996). A quimioterapia de alta-dose, que pode estar associada à retirada de células progenitoras hematopoiéticas, é uma opção terapêutica curativa para pacientes com neoplasias onco-hematológicas (BEWARDER et al., 2018).

Nesse contexto, o transplante de células-tronco hematopoéticas (TCTH) se trata de um procedimento complexo que utiliza quimioterapia de alta dose e possui grande potencial de cura para pacientes diagnosticados com diversas doenças, não apenas onco-hematológicas, mas também algumas deficiências imunológicas e doenças metabólicas. Ele consiste na infusão de células progenitoras obtidas de um doador compatível, quando for do tipo alogênico, cujo objetivo é a remissão da doença.

No entanto, quando essas células forem removidas da própria medula do paciente antes das doses elevadas de quimioterapia, chamamos de TCTH autólogo.

Como o tratamento citotóxico não engloba somente a quimioterapia em altas doses, a radioterapia através da irradiação corporal total pode estar presente em alguns tipos de condicionamento do TCTH alogênico. Assim, o acúmulo de diversos tratamentos favorece o surgimento de muitos efeitos colaterais. As repercussões mais conhecidas são relacionadas a quimioterapia, como náuseas e vômitos, redução da ingesta alimentar, fraqueza generalizada, indisposição, fadiga e redução das atividades de vida diária (AVDs) (COPELAN E.A., 2006; ARNAOUT K. et. Al., 2014). Outros efeitos mais relacionados ao tratamento pré-transplante incluem infecções, anemia e sangramento associado a plaquetopenia. Já as complicações após a recuperação da medula se resumem à doença do enxerto contra o hospedeiro (DECH) e infecções devido disfunção imunológica. Com isso, internações hospitalares mais prolongadas podem ser necessárias, principalmente nos casos de TCTH alogênico e com complicações mais graves, como distúrbios de mucosa, infecções bacterianas, fúngicas e cistite hemorrágica. Isto contribui para consequências físico-funcionais, como redução da capacidade funcional, da força muscular, mobilidade e independência (ARNAOUT K. et. al, 2014).

Portanto, pacientes submetidos ao TCTH apresentam redução do nível de atividade física devido às altas doses de quimioterapia e/ou iradiação corporal total utilizadas desde o tratamento pré-TCTH. Como resultado, funções físicas relacionadas à força e resistência muscular estarão afetando as atividades da vida diária (AVD) e a qualidade de vida (QV) destes pacientes. A reabilitação se torna essencial para melhorar o nível de atividade física, os distúrbios motores, a fadiga e QV associados ao tratamento com TCTH (MORISHITA S., et al., 2013; TAKEKIVO T. Et. al, 2015; ISHIKAWA A. Et.al, 2019).

1.1.1 Fadiga

A fadiga aos esforços é uma das queixas mais comuns nesta população, ocorrendo devido redução no número de células sanguíneas. Os efeitos sistêmicos provocados pela quimioterapia, associada aos da doença de base, tornam a fadiga um dos sinais mais prevalentes (STEINBERG et al., 2015).

A fadiga relacionada ao câncer (FRC) é definida como sensação de cansaço que não ameniza com o repouso, o que acaba influenciando em outros desfechos como funcionalidade e tolerância ao exercício. Trata-se de uma queixa menosprezada em meio a tantas outras preocupações com o tratamento, como probalidade de cura, exames laboratoriais, chances de recidiva, infecções e medicações. Os tratamentos agressivos, que não apenas destroem células tumorais mas atingem tecidos saudáveis, são os responsáveis iniciais desta manifestação onco hematológica. Salienta-se que a fadiga engloba aspectos muito além do físico, como mental e social, e que o principal modo de manejo é o não-farmacológico. (WISKEMANN et al., 2010).

Os modos de diagnóstico e monitoramento são realizados através de questionários subjetivos ou escalas. Os mais comumente encontrados são: *Multidimensional Fatigue Inventory* (MFI), EORTQ-QLC fatigue subscale, *Revised Piper Scale*, *Facit-F*, *FACT-F, Lasa*, *FAS*, *FAQ*, *Facit-an*, and PROMIS (PENNA et.al., 2023).

A maioria dos estudos tem utilizado o MFI como abordagem para diagnóstico da FRC. É um questionário breve e autoaplicável, originalmente desenvolvido em holandês, utilizado especificamente para a avaliação da fadiga no linfoma de Hodgkin, elaborado por Smets et al., (1996), traduzida e validada para o Brasil por Baptista et al. (2012). O questionário é composto por 20 itens organizados em cinco escalas, relacionados a diferentes dimensões da fadiga: 1) fadiga geral, 2) fadiga física, 3) fadiga mental, 4) redução da atividade e 5) redução da motivação. Cada escala é composta por quatro itens, dois indicativos e dois contra indicativos de fadiga. Todos os itens são respondidos em uma escala de cinco pontos (1= “Sim, é verdade” e 5="Não, não é verdade"). A pontuação é calculada para cada escala, variando de quatro a vinte, com as pontuações mais altas indicando níveis mais elevados de fadiga. A pontuação total é obtida a partir da soma das cinco dimensões distribuídos em 4 dimensões (sensorial, afetiva, comportamental e cognitiva/emocional).

1.1.2 Desempenho físico

Outra repercussão que carece atenção durante o tratamento citotóxico é a função física, que ainda pode ser chamada de funcionalidade ou desempenho físico. Sua avaliação pode ser realizada de diversas formas, dependendo do objetivo terapêutico para o paciente, fase do tratamento e também espaço físico. O Teste de

Caminhada de Seis Minutos (TC6) é muito utilizado na população onco hematológica, principalmente no TCTH. Devido a sua necessidade de espaço físico e a necessidade dos pacientes permanecerem em isolamento na internação hospitalar, algumas alternativas são necessárias. Testes de capacidade funcional ou tolerância ao exercício são empregados neste contexto, como o Teste do Degrau de Dois Minutos (TD2) e o Teste do Senta e Levanta de 30 segundos (TSL30), que ainda pode ser utilizado para mensurar força indireta de membros inferiores (MORISHITA, 2029)

Quando há possibilidades de avaliações mais completas, visando pesquisa científica ou dados mais exatos, é utilizada a dinamometria para avaliar força muscular, tanto para membros inferiores quanto para superiores ou preensão palmar (ALMEIDA et. al, 2019). A avaliação da força de membros superiores é realizada através do teste de força de preensão manual, que tem sido correlacionada com outros desfechos, como qualidade de vida (MUSALEK, C., 2017; PARRA-SOTO S., 2022). E para avaliar a força muscular de membros inferiores pode ser utilizado dinamômetro digital principalmente para musculatura extensora de joelho na posição sentada (YEUNG, S.S.Y., 2018).

2.1 REABILITAÇÃO FÍSICA ONCO HEMATOLÓGICA

O exercício físico é uma terapia adjuvante para sobreviventes do câncer e tem demonstrado resultados favoráveis. As pesquisas realizadas no âmbito da oncologia e da reabilitação física abrangem, na maioria dos trabalhos, a população que sobrevive ao tratamento e que, portanto, apresentam as complicações observadas mais tardiamente. Propor a prática de exercício físico para pacientes em quimioterapia é um grande desafio pelo fato de que no início do tratamento estes pacientes enfrentam tanto os efeitos paraneoplásicos da doença de base quanto os efeitos colaterais oriundos do tratamento citotóxico que geralmente agride simultaneamente múltiplos órgãos e sistemas. Iniciar o exercício físico antes que estes efeitos deletérios se instalem pode propiciar ao paciente maior segurança, conforto e adesão à reabilitação física. Além disso, há também uma boa chance de que o início precoce pode evitar ou amenizar o desconforto ao esforço durante as sessões de treinamento (CAMPBELL, K. L., WINTERS-STONE, K. M., WISKEMANN, J., et al., 2019). Por isso, a conduta de iniciar o protocolo precocemente seria uma opção para aumentar a adesão. Há estudos que demonstram bons resultados clínicos com pacientes realizando reabilitação até mesmo antes do início da quimioterapia ou do transplante de células-tronco hematopoiéticas, como forma de pré-condicionamento físico com vistas ao aumento da capacidade funcional e tolerância ao longo tratamento (GONZALO-ENCABO, P., WILSON, R. L., KANG, D. W., NORMANN, A. J., DIELI-CONWRIGHT, C. M., 2022).

O exercício físico é considerado como modalidade de tratamento para algumas complicações relacionadas ao taratamento onco-hematológico, principalmente nas alterações físico funcionais ligadas à manifestação e exacerbação da fadiga oncológica. (GONZALO, P. et al., 2022; SALERNO, E. A. et al., 2021; PENNA, G. B. et al., 2023) Os benefícios já estão claramente estabelecidos na oncologia, mas o emprego do exercício físico de forma adjuvante à quimioterapia enfrenta diferentes obstáculos operacionais, principalmente em relação ao acesso a programas específicos de reabilitação física em oncologia, estruturados com periodização indicada para a prevenção dos efeitos deletérios envolvidos com a redução da funcionalidade e as limitações impostas pela intolerância ao esforço e a manifestação precoce de fadiga.

Mesmo na presença de complicações, a terapia com exercícios deve ser continuada o máximo possível, com base em uma avaliação completa, e rigorosidade em relação aos exames laboratoriais. A avaliação durante a hospitalização para TCTH é geralmente realizada antes e após o TCTH, o que muitas vezes torna-se desafiador devido a condição física deficitária já instalada, fadiga e presença de cateteres intravenosos. A avaliação da função física inclui força muscular, tolerância ao exercício, capacidade de caminhar ou mobilidade, flexibilidade e equilíbrio. As avaliações pré-TCTH são realizadas logo após a admissão para o TCTH, e as avaliações pós-TCTH são realizadas após a recuperação medular ou quando o paciente recebe alta hospitalar (TAKEKIYO T, 2015; TAKEKIYO T, 2023; ISHIKAWA A, 2019; WISKEMANN J, 2011).

Relatos sobre terapia com exercícios antes e depois do transplante começaram a aumentar a partir da década de 1990. Nos últimos anos, foi relatado que ela é segura e viável para reabilitação realizada antes da admissão para TCTH. Em relação aos benefícios da terapia com exercícios em pacientes submetidos a TCTH, o exercício físico, incluindo exercícios aeróbicos, treinamento de resistência e exercícios de alongamento tem demonstrado afetar positivamente a saúde fisiológica, psicológica e psicossocial (WISKEMANN J, 2011; VAN HAREN, 2018; LYANG Y, 2018).

2.1.1 Modalidades e tipos de sobrecarga muscular

A reabilitação onco hematológica abrange diversas intervenções necessárias para recuperar o paciente de todos efeitos colaterais sofridos. Portanto, necessita abordagem de equipe multiprofissional nesse processo tão complexo. A reabilitação física ou funcional é composta de uma prescrição personalizada de exercícios físicos condizentes com as necessidades detectadas na avaliação prévia do paciente. Definido os objetivos, o profissional fisioterapeuta pode planejar qual tipo ou modalidade de exercício físico beneficia mais o paciente, seja aeróbio, resistido, de força, combinado, flexibilidade ou equilíbrio (KNIPS, 2019; DUREGON et al.,2019).

As variações de intensidade geram obstáculos devido a equilibração entre riscos e benefícios. A classificação de intensidade para exercício físico pode ser considerada leve, moderada ou alta. A sua regulação pode ser feita através da escala Borg, do *talk test* ou pelo cálculo da frequência cardíaca máxima. A intensidade leve torna-se a mais confortável para o paciente em quimioterapia de alta dose pois além de alterar menos os sinais vitais, gera menos cansaço (PERSOON et al., 2013; WEHRLE et al., 2019). No entanto, intensidades moderadas podem beneficiar mais os pacientes quando avaliado os desfechos de FRC e capacidade funcional. Além disso, alguns estudos destacam a importância da manutenção da regularidade da prática dos exercícios físicos, com a adequada adaptação conforme a oscilação dos exames laboratoriais, disposição e motivação do paciente. Nem sempre a exposição prolongada ao exercício será a mais eficaz no tratamento, mas a prescrição ajustada da frequência semanal, volume de treinamento baseado em séries, repetições e peso são de extrema importância para obtenção de resultados positivos (OECHSLE, 2014).

2.1.2 Reabilitação durante a internação hospitalar para o transplante de células-tronco hematopoéticas

A terapia com exercícios em pacientes submetidos a TCTH alogênico também tem um impacto positivo na sobrevida pós-alta. Jones et al. (2015) relataram que uma distância percorrida no teste de caminhada de 6 minutos (TC6M) antes do transplante de ≥ 400 m forneceu informações adicionais sobre a predição da sobrevida global com ajuste de idade.

Em contraste, uma distância percorrida no TC6M < 400 m antes do transplante e uma diminuição na distância percorrida no TC6M antes e depois do transplante estão associadas a um alto risco de mortalidade não relacionada à recidiva após TCTH alogênico. Acredita-se que a terapia com exercícios em receptores de TCTH tenha um impacto positivo na manutenção da função física, qualidade de vida e sobrevida após o transplante (Wiskemann J, 2015; JONES LW, 2015).

As intervenções para controle dos sintomas frequentemente são implementadas após serem submetidos ao TCTH, o que agrava mais a FRC e o desempenho físico, tornando difícil sua reversão. Provavelmente isto deve-se ao fato de que a realização de exercícios físicos neste período causa desconforto e desconfiança quanto a sua segurança. A prevenção ou até mesmo intervenções durante a internação parecem ser opções factíveis e muito eficazes para o manejo da fadiga durante o tratamento citotóxico. A segurança para realização da reabilitação física ocorre pela verificação rotineira dos exames laboratoriais e avaliação clínica criteriosa diária do profissional responsável. Valores limítrofes de hemoglobina e plaquetas não devem ser barreiras para a reabilitação, mas motivo para readaptação do planejamento e comunicação com os demais membros da equipe. Tratamentos prévios, internações prolongadas e falhas terapêuticas são alguns fatores que que desafiam o profissional para implementar a terapêutica adequada (WEHRLE et al., 2019; (ALMEIDA et. al, 2019).

Neste sentido, Sasso et al., (2015) recomendam que a prescrição do exercício seja individual e baseada na resposta cardiorrespiratória, força muscular; sobrecarga progressiva e período de recuperação suficiente para oferecer descanso apropriado à fim de otimizar as adaptações fisiológicas promovidas pela sobrecarga muscular especifica do programa de reabilitação. Fairman et al. (2017), ampliam este conceito, integrando variáveis fundamentais do treinamento de resistência, que subsidiam as adaptações ao estímulo de sobrecarga muscular dentro de um programa de reabilitação baseado nos conceitos de periodização variável de volume, intensidade e frequência do esforço físico.

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2 OBJETIVOS

Este estudo tem como objetivo avaliar os efeitos da reabilitação física na fadiga relacionada ao câncer em diferentes fases do tratamento citotóxico antineoplásico.

Os objetivos específicos incluíram:

1) Avaliar os efeitos da fisioterapia na fadiga relacionada ao câncer durante o tratamento citotóxico.

Artigo 1: Physical rehabilitation for the management of cancer-related fatigue during cytotoxic treatment: a systematic review with meta-analysis

2) Comparar o efeito de três modos de reabilitação física sobre a fadiga relacionada ao câncer (FRC) de pacientes hospitalizados para o transplante de células-tronco hematopoéticas (TCTH).

Artigo 2: Exercício físico intra-hospitalar para o manejo da fadiga relatada por pacientes submetidos ao transplante de células-tronco hematopoiéticas

3 ARTIGO 1 (Publicado no periódico *Supportive Care in Cancer* , Fator de Impacto 3.0)

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REVIEW

Physical rehabilitation for the management of cancer-related fatigue during cytotoxic treatment: a systematic review with meta-analysis

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Abstract
Objective To assess the effect of physical therapy on cancer-related fatigue (CRF) during cytotoxic anticancer treatment.
Methods Systematic review with meta-analysis of randomized clinical trials published from 2010 to 2021 (EMBASE, MEDLINE, PEDro; SciELO, and LILACS). Studies assessing the effect of supervised physical therapy (IG) for the management of CRF on adults undergoing anticancer treatment compared with a control group (CG) covering usual care or any uncontrolled practice, such as recommendations about exercise and health education, were included in this review.
Results A total of 22 studies were included in the SR and 21 in the meta-analysis, resulting in 1.992 individuals (CG = 973 and IG = 1.019). There was a reduction in general fatigue [SMD = − 0.69; 95%CI (− 1.15, − 0.22) $p < 0.01$; $I^2 = 87\%$; NNT = 3], with greater weight attributed to combined exercise (44%). Physical fatigue also reduced [SMD = − 0.76; 95%CI (− 1.13, − 0.39) $p < 0.01$; $I^2 = 90\%$; NNT = 2], with greater weight for resistance exercise (50%) and greater effect with combined exercise [SMD = − 1.90; 95%CI (− 3.04, − 0.76) $p < 0.01$; $I^2 = 96\%$]. There was reduction in general fatigue with moderate intensity (74%) [SMD = − 0.89; 95%CI (− 1.61, − 0.17) $p < 0.02$; $I^2 = 90\%$] and physical fatigue [SMD = − 1.00; 95%CI (− 1.54, − 0.46) $p < 0.01$; $I^2 = 92\%$], while high intensity reduced only general fatigue [SMD = − 0.35; 95%CI (− 0.51, − 0.20) $p < 0.01$; $I^2 = 0\%$]. The number of overall and weekly sessions has been shown to contribute to the reduction of CRF.
Conclusion Physical rehabilitation with moderate intensity promoted greater relief of general and physical fatigue. Even after controlling for high heterogeneity, the quality of evidence, summarized in GRADE, was considered moderate for general fatigue and low for physical fatigue.

Keywords Physical and rehabilitation medicine · Physical therapy · Chronic fatigue syndromes · Patient outcome assessment · Antineoplastic agents

Introduction

Cancer-related fatigue (CRF) is one of the symptoms affecting cancer patients. It manifests itself from the dysfunctions resulting from the underlying disease itself, but mainly from the systemic side effects arising from the antineoplastic treatment. There are multiple factors associated with CRF, which range from function changes of central and peripheral nervous systems to dysregulation in hematological, metabolic, and energetic activity [1, 2].

It includes subjective aspects of feeling physical and emotional weariness which are not proportional to the physical activity performed [1]. It can also manifest due to overlapping pre-existing comorbidities or side effects associated with polypharmacy, physical deconditioning, mood swings,

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emotional distress, and sleep disturbances that can worsen symptoms [3, 4].

Various scales are used to assess fatigue, some of which separate general from physical fatigue in order to distinguish behavioral, mental, and emotional aspects from components explicitly related to physical-functional characteristics. However, regardless of the criteria used, CRF is usually characterized by a slow reversal of the feeling of weariness by remaining at rest [5].

The treatment of CRF may include pharmacological [6] and non-pharmacological [7, 8] therapies, such as integrative therapies [9], multimodal [10], and physical exercise [11, 12], which are part of the physical therapy planning, especially when individuals are in the period the antineoplastic treatment causes side effects. Pharmacological therapies do not demonstrate the same efficacy when compared to non-pharmacological treatment [13]. Although interventions with passive techniques are apparently more comfortable for patients, therapies that involve properly prescribed physical effort continue to be the most indicated [14, 15]. The systemic effects and the benefits promoted by regular physical exercise in the oncological scenario are widely described [16, 17]. A rehabilitation program can consist of different schemes for physical exercises, both aerobic and resistance, or even a combination of both. It is considered physical rehabilitation because it combines aspects of both musculoskeletal and cardiopulmonary systems. Although there is variety of literature on the management of CRF, it is still possible to identify some gaps in this area, especially in the acute phase of cytotoxic treatment (chemotherapy and radiotherapy), such as further details about muscle overload, intensity of effort, and the duration of the physical rehabilitation program. Available data gathers older studies carried out at a time [13] when anticancer protocols had not been undergone to recent updates.

Early studies showed that even in antineoplastic treatment, musculoskeletal adaptations occur with different muscle overloads. While the most intense overloads develop the contractile structure of the muscle fiber, the moderate ones increase the oxidative capacity and the ratio of the number of capillaries per muscle fiber [18]. These results encourage the use of physical rehabilitation during cytotoxic treatment, even in the most aggressive [19]. Considering the constant updates in the antineoplastic protocols, the accumulation of knowledge about rehabilitation in the acute phase of the cytotoxic treatment, and the variability of the structuring characteristics of the rehabilitation protocols (type and intensity of effort), this study intends to continue the analysis of the effect of physical rehabilitation on CRF during the acute phase of cytotoxic treatment (primary outcome). As a secondary outcome, the types of muscle overload (aerobic, resistance, and combined) and the intensity of the effort (light, moderate, and high) developed in the phase in which the antineoplastic treatment reaches the apex of the manifestations related to general and physical fatigue were analyzed. This study describes central details of the elements that make up the physical therapy protocol used for the management of CRF.

Methods

This systematic review was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline [20] and registered on Prospectively registered systematic reviews in health and social care (PROSPERO), under register CRD42018096547. The primary outcome is CRF (general and physical fatigue). At the same time, the types of muscle overload (aerobic, resistance, and combined) and the intensity of effort (light, moderate, and high) were considered the secondary outcomes.

Search strategies

Randomized clinical trials (RCTs) published from 2010 to 2021 in Portuguese, English, and Spanish available in the databases of the *National Library of Medicine* (MEDLINE and PUBMED), Ovid MEDLINE®, *Physiotherapy Evidence Database* (PEDro), Excerpta Medica dataBASE (EMBASE), *Scientific Electronic Library Online* (SciELO), and *Latin American and Caribbean Health Sciences Literature* (LILACS). The search took place in September 2021 and was structured according to the PICO strategy through the descriptors. The following keywords were used: “Physiotherapy,” “Physical Therapy Modality,” “Cancer,” “Neoplasia,” “Muscular fatigue.” The complete strategy is in the supplementary material. Boolean operators “*OR*” and “*AND*” were used to combine search terms. The filter for “randomized clinical trials” was used according to each of the different databases. There was no directed manual search in a grey literature database.

Eligibility criteria

Only RCTs (complete and published) performed with individuals aged 18 years or older in the acute phase of cytotoxic anticancer treatment (chemotherapy, radiotherapy, or both) were included. It was included studies which divided the volunteers during the cytotoxic treatment into a group with physical therapy performed in person (intervention), while in the other group (control) the subjects should be treated with usual care or any uncontrolled practice, such as recommendations about exercise and health education.

Activities with non-face-to-face supervision, such as telephone monitoring or cognitive behavioral approach, were excluded from the study. Passive therapies with massage, meditation, and acupuncture, and activities that did not demonstrate a pattern of muscle overload and intensity such as Yoga, Tai Chi, Qigong, and hydrotherapy were also excluded from this research. In addition, lung-specific therapies in which there was no peripheral muscle overload, such as respiratory muscle training, were also excluded from the analysis. Interventions with individuals in advanced stages of cancer (terminal patients), on hormone therapy alone or during the cytotoxic post-treatment follow-up phase were excluded. From the follow-up studies, only information regarding the acute phase of the cytotoxic treatment.

Selection of studies and data extraction

Two independent reviewers (TS, DM) excluded studies after reading titles and abstracts in Mendeley® software. The remaining articles were thoroughly assessed, and the selected ones underwent systematic data extraction and storage. Disagreements between evaluators were solved by a third evaluator (GP). Physical fatigue was extracted from the questionnaires containing a subcategory related to the physical aspects of the feeling of fatigue. The intensity of physical effort was considered according to the description provided by the authors in the protocols of each study, and they were classified as mild, moderate, or high.

Risk of bias assessment

The risk of bias was assessed as proposed by the *Cochrane Handbook for Systematic Reviews of Interventions* [20] by two independent investigators (GP, DM). Disagreements were discussed with the third investigator for a final decision. For each criterion, judgment was made as low risk, high risk, *or* unclear *risk of bias*.

Data synthesis and analysis

DerSimonian and *Laird* random effects model, adjusted by the Hartung-Knapp method, with 95% confidence intervals. All analyses were conducted using RStudio software (version 1.3.1093), with statistical packages "meta" and "dplyr" implemented in version R 3.6.2 (R Project for Statistical Computing).

The standardized mean difference (SMD) was used to combine results from different fatigue measurement units. The grouped standard deviations were calculated as recommended by the adjusted G Hedges method. To ensure that all scales pointed in the same direction, we multiplied the mean values by −1 from studies in which fatigue severity decreased with higher scores [21–26]. Two studies reported no post-treatment standard deviations [27, 28], in which case we imputed a reasonably high value based on the standard deviations obtained from the post-treatment means of other studies included in this meta-analysis. SMD up to 0.2 was considered to be of small effect size, between 0.2 and 0.8 moderate, and above 0.8 large. The number needed to treat (NNT) was calculated from the SMD [21, 29, 30].

The overall quality of evidence was determined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [31]. For general fatigue and physical fatigue outcomes, the quality of evidence was considered as "high" and subsequently reduced to "moderate," "low," and "very low" depending on the criteria.

To identify potential sources of heterogeneity and effect modifiers, we performed subgroup analyses for categorical covariates based on the following: (a) exercise intensity and (b) exercise type. For continuous covariates (program duration in weeks, session duration in minutes, number of sessions per week, and total number of sessions over the intervention period), we performed univariate meta-regression analyses. Sensitivity analyses were used to identify and exclude *outliers* with disproportionate influence on the other studies grouped in the primary analyses. The evaluation of publication bias was performed through visual inspection of funnel plots and Egger regression.

Results

Description of studies

In the initial search, 799 studies were found. Of these, 100 were excluded due to duplicity, 348 due to titles, and 245 after analyzing the abstracts. Of the 106 studies analyzed, 22 met all the inclusion criteria and entered the analysis (Fig. 1). Of these 22 articles, only one was not included in the meta-analysis due to the graphical presentation of the results, which made it impossible to extract fatigue values for statistical analysis. The authors were consulted via e-mail, but no response was obtained.

In total, 1,992 individuals (53.9±8.1 years) participated in the RCTs, 1,019 in the intervention group and 973 in the control group (Table 1). The characteristics of the included studies are detailed in Table 1. Among the interventions, 4 studies assessed aerobic exercises [32–35], 9 performed exclusively resistance exercises [22–24, 34–39], and 11 combined both modalities [25–28, 40–46]. The most prevalent diagnosis was breast cancer (41%) [23, 24, 32, 33, 35, 36, 41, 43, 45] followed by hematological malignancies (18.2%) [22, 38, 40, 46], prostate cancer (13.6%) [26–28], head and neck (9.1%) [33.42], various tumors (9.1%) [30.36], colon (4.5%) [44], and lung (4.5%) [34]. The intervention was performed during chemotherapy in 11 studies [22, 23, 25, 32–35, 43–46], 6 during radiotherapy [24, 26–28, 37, 39] and in 5 studies, patients underwent both types of cytotoxic treatment [36, 38, 40–42]. In 2 articles, aerobic exercise was

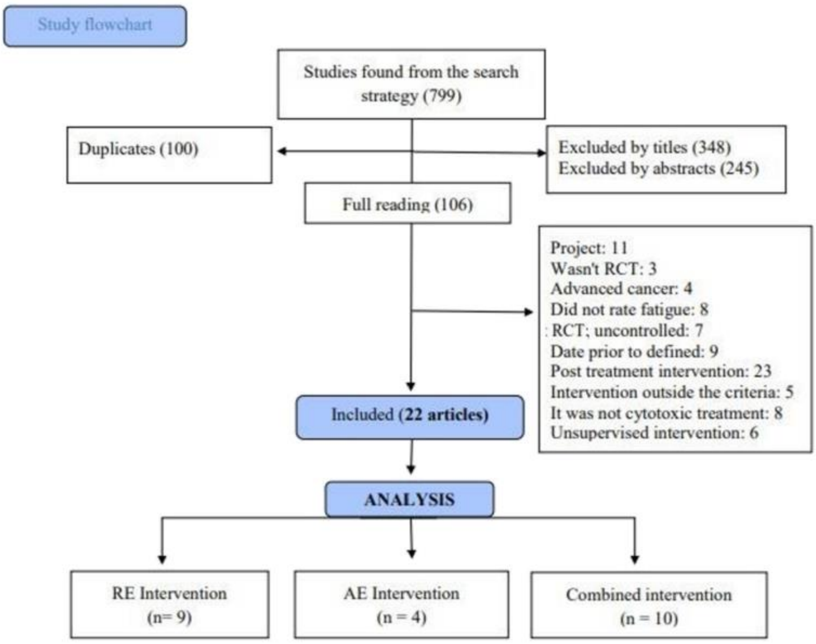

Fig. 1 Study selection process. RE = resistance; AE = aerobic; RCT = randomized controlled trial

compared to resistance and to the control group [33, 35]. The intervention time ranged from 6 to 18 weeks; weekly frequency ranged from 2 to 8 sessions, while the session duration was between 30 and 120 min.

Assessment instruments

CRF was assessed by 10 different instruments. The most used scale was the *Multidimensional Fatigue Inventory* (MFI) (22%) [37, 43–46], followed by the EORTQ-QLC fatigue subscale (18.1%) [22, 36, 38, 40], Revised *Piper Scale* (13.6%) [32, 33, 35], *Facit-F* (9%) [27.38], *FACT-F* (9%) [39.40] *Lasa* (9%) [34.42], *FAS* (4.5%) [39], *FAQ* (4 .5%) [24], *Facit-an* (4.5%) [25], and PROMIS (4.5%) [41]. In 12 studies, physical fatigue was evaluated in subscales described as "physical fatigue" [22–24, 37, 38, 43, 44], "behavioral fatigue/daily life" [33, 35], and "physical well-being" [27, 28, 39].

Outcome assessment

Figure 2 presents the results for the main outcome of the study (general fatigue Fig. 2A, 23 studies and physical fatigue Fig. 2B, 14 studies). In the general analysis, considering all the studies that tested the effect of the intervention with physical exercise during the cytotoxic treatment for different neoplasms, there was a reduction in the feeling of general fatigue when compared to the SMD control group: [−0.69; 95%CI (−1.15, −0.22) $p<0.01$; $I^2=87\%$; NNT=3]. The greatest weight for this result was attributed to interventions that used combined physical exercise (44%), followed by exclusively resistance exercises (39%). Only 17% of the effect was attributed to studies that used aerobic exercises exclusively, however, in the analysis between groups, no difference was observed (Chi^2: 2.77, dif.=2, $p=0.25$). In the subset of the information provided by the 4 studies that used exclusively aerobic exercises, general fatigue was not different from the control group. Heterogeneity was significantly high in protocols with combined physical exercise, especially in the studies by Hojan et al. (2016) and Hojan et al. (2017) [39.40]. On the other hand, in the subgroup that used exclusively resistance exercises, practically, no heterogeneity was detected.

The results of the meta-analyses performed to assess physical fatigue (Fig. 2B) indicate that, in the combined analysis, the intervention with physical exercise reduced the sensation of physical fatigue [SMD=−0.76; 95%CI (−1.13, −0.39) $p<0.01$; $I^2=90\%$; NNT=2]. The highest weight was attributed to those who used exclusively resistance physical exercise (50%), followed by combined exercises (34%) and aerobic exercises (16%). In the analysis of subgroups, there was a difference between the types of muscle overload (Chi^2: 8.64, dif.=2, $p=0.01$), because the combined exercise alone promoted a reduction in physical fatigue [SMD=−1.90; 95%CI (− 3.04, −0.76) $p<0.01$; $I^2=96\%$].

Table 1 Characteristics of the included studies

Author (n)	Clinical information	Intervention(I) X Control(C)	Outcome of interest/general results
Al-Majid, S et al. 2015 $n=14$	Breast cancer Chemotherapy	I($n=7$) treadmill aerobic exercise (12 weeks; 3×/week; 40 min/session with moderate intensity) C($n=7$) = usual care	Questionnaire: PIPER Exercise during chemotherapy may protect against chemotherapy-induced decline in VO2max but not hemoglobin concentration
Bolam, KA et al. 2019 $n=206$	Breast cancer Chemotherapy	I($n=72$) continuous aerobic exercise, 3 sets of 3 min HIIT on cycle ergometer (1 min break), (16 weeks; 2×/week; 60 min/session with moderate intensity) C($n=60$) printed guidance on physical activity	Questionnaire: PIPER In the RT-HIIT group, CRF was lower and lower limb muscle strength was greater than in the control at 2 years. In the AT-HIIT group, the symptoms were significantly lower
Dhillon, HM et al. 2017 $n=111$	Lung cancer Chemotherapy	I($n=56$) aerobic exercise; nutritional orientation (8 weeks; 8×/week; 60 min/session with undetermined intensity) C($n=55$) routine monitoring and nutritional guidelines	Questionnaire: FACIT-F There was no significant difference in fatigue at 2, 4, or 6 months, in QOL, symptoms, physical status, or survival
Mijhel, S, et al. 2017 $n=206$	Breast cancer Chemotherapy	I($n=60$) warm up exercises; aerobic exercise on a treadmill or cycle ergometer and relaxation. (16 weeks; 2×/week; 60 min/session with moderate intensity) C($n=57$) written information about physical exercise	Questionnaire: PIPER There was improvement and maintenance of vital aspects of QoL
Bolam, KA et al. 2019 $n=206$	Breast cancer	I($n=74$) resistance exercises; 2 sets of 8–12 rep; 3 sets of 3 min of HIIT on a cycle ergometer (1 min of	Questionnaire: PIPER
	Chemotherapy	break), (16 weeks; 2×/week; 60 min/session with moderate intensity) C($n=60$) written information about physical activity	There was improvement in cancer-related total and cognitive fatigue and an increase in lower limb muscle strength
Cešeiko, R et al. 2019 $n=55$	Breast cancer Chemotherapy and radiotherapy	I($n=27$) warm up exercises; 4 sets of 4 rep. (leg press with progressive load), (12 weeks; 2×/week; 40 min/session and moderate intensity) C($n=28$) weekly orientation (telephone) to perform 3 sets of 10 repetitions of sitting and rising from a chair	Questionnaire: EORTC QLQ-C30 There was improvement in muscle strength, QoL and reduction in fatigue after a 12-week high-intensity strength training program
Grote, M et al. 2018 $n=20$	Varied tumors Radiotherapy	I($n=10$) bicycle warm up; 3 sets of 8—12 rep. of resistance exercises (1 min of break) and progressive load at each session; 6 weeks; 3×/week; 30 min/session with undetermined intensity C($n=10$) usual care	Questionnaire: MFI No significant benefit on fatigue and QOL was found, but results were better for general fatigue and QoL in the intervention group
Kacker, ED et al. 2011 $n=19$	Malignant hematological diseases Chemotherapy	I($n=09$) progressive resistance exercises; 8 exercises with elastic band and 3 using own body weight (6 weeks; 3×/week; undetermined session time and moderate intensity C($n=10$) recommendations about rest and physical activity	Questionnaire: EORTC QLQ-C30 This study demonstrates the positive effects of strength training on physical activity, fatigue, and quality of life in people receiving high-dose chemotherapy and HSCT
Kacker, ED et al. 2017 $n=67$	Malignant hematological diseases Chemotherapy and radiotherapy	I($n=33$) progressive resistance exercises; 8 exercises with elastic band and 3 using own body weight (6 weeks; 3×/week; undetermined session time and moderate intensity C($n=34$) usual care; health education	Questionnaire: EORTC QLQ-C30 A 6-week moderate-intensity strength training intervention improves early recovery after HSCT, reducing fatigue while maintaining and/or improving muscle strength and functional capacity

Table 1 (continued)

Author (n)	Clinical information	Intervention(I) X Control(C)	Outcome of interest/general results
Mijhel, S et al. 2017 $n=206$	Breast cancer Chemotherapy	I($n=65$) Resistance exercises; major muscle groups; 2–3 sets of 8–12 rep; (16 weeks; 2×/week; 60 min/session and moderate intensity) C($n=57$) Written information about physical activity	Questionnaire: EORTC QLQ-C30 Physical training with HIIT reduced CRF and symptoms during chemotherapy, improving or maintaining vital aspects of HRQoL
Rogers, LQ et al., 2012 $n=13$	Head and neck tumor Radiotherapy	I($n=07$) 9 progressive resistance exercises (10 rep); elastic bands and own body weight; major muscle groups. (12 weeks; 2×/week; 60 min/session and moderate intensity) C($n=08$)) No specific recommendation	Questionnaire: FAS Resistance exercise is safe and feasible in head and neck cancer patients receiving radiation
Schmidt, ME et al., 2014 $n=95$	Breast cancer Chemotherapy	I($n=49$) 8 progressive resistance exercises; 3 sets of 8–12 rep (12 weeks; 2×/week; 60 min/session and moderate intensity) C($n=46$) muscle relaxation	Questionnaire: LASA Resistance exercise improved fatigue during chemotherapy. The early start of exercise prevents loss of strength and aggravation of fatigue and physical inactivity
Steindorf, K et al., 2014 $n=155$	Breast cancer Radiotherapy	I($n=77$) 8 progressive resistance exercises; 3 sets of 8–12 rep (12 weeks; 2×/week; 60 min/session and moderate intensity) C($n=78$) muscle relaxation	Questionnaire: FAQ Resistance exercises are safe, feasible, and effective to improve CRF and QoL components in patients undergoing adjuvant radiotherapy
Andersen, C et al. 2013 $n=213$	Varied tumors Chemotherapy	I($n=106$) Warm up exercises; 4 resistance exercises and cardiovascular training; cool-down (6 weeks; 4×/week; 120 min/session and intense intensity) C($n=107$) Conventional medical care without physical restrictions	Questionnaire: FACIT-AN Supervised multimodal exercise leads to significant benefits in the self-reported perception of patients with CRF, but not in the patients' general quality of life score
Baumann, F. T Et. Al 2011 $n=33$	Malignant hematological diseases	I($n=17$) Aerobic exercise on a cycle ergometer (continuous), (8 weeks; 7×/week; 45 min/session and intense intensity) C($n=16$) Conventional physical therapy with low- intensity active and passive mobilization	Questionnaire: EORTC QLQ-C30 The training program is feasible and to have positive influence on physical performance and quality of life in patients undergoing allogeneic HSCT
	Chemotherapy and radiotherapy		
Cormie, P et al. 2015 $n=63$	Prostate cancer Radiotherapy	I($n=32$) Warm up exercises; Cardiovascular exercise; 8 resistance exercises; main muscle groups of upper and lower limbs; 1–4 sets of 6–12 rep progressively (12 weeks; 2×/week; 60 min/session and moderate intensity) C($n=31$) Usual care	Questionnaire: FACIT-F Mixed exercise when initiating androgen suppression therapy reduces the severity of adverse changes in body composition, physical function, total cholesterol, sexual function, fatigue, and psychological distress
Hojan, K et al. 2016 $n=55$	Prostate cancer Radiotherapy	I($n=27$) Warm up exercise; Aerobic exercise on a treadmill or bicycle; 5 resistance exercises; 2 sets of 8 rep C($n=27$) Activities of daily living. (8 weeks; 5×/week; 55 min/session and moderate intensity)	Questionnaire: FACT-F Moderate exercise during radiotherapy and hormone therapy improves functional capacity and concentrations of inflammatory markers, decreases fatigue, and improves quality of life

Table 1 (continued)

Author (*n*)	Clinical information	Intervention(I) X Control(C)	Outcome of interest/general results
Hojan, K et al. 2017 $n=72$	Prostate cancer Radiotherapy	I($n=35$) Warm up exercise; Aerobic exercise (brisk walking, cycling, or treadmill); five resistance exercises; 2 sets of 8 rep (8 weeks; 5×/week; 55 min/session and moderate intensity) C($n=31$) Usual activities of daily living	Questionnaire: FACT-F Long-term supervised exercise is more effective than physical activity educational materials in reducing cardiovascular risk and improving functional and emotional state or fatigue
Rogers, LQ et al. 2014 $n=44$	Breast cancer Chemotherapy and radiotherapy	I($n=20$) Aerobic exercise (moderate-intensity walking); eight resistance exercises; major muscle groups; 2 sets of 15 rep (10 weeks; 2×/week; 40 min/session and moderate intensity) C($n=22$) Usual activities of daily living	Questionnaire: PROMIS Biobehavioral factors enhanced the effects of the intervention on fatigue, while psychosocial factors predicted the fatigue response
Samuel, RS et al. 2019	Head and neck tumor	I($n=58$) Aerobic exercise (walking); resistance exercises; main muscles of the upper and lower	Questionnaire: LASA
$n=120$	Chemotherapy and radiotherapy	limbs; 2 sets of 8 to 15 rep (11 weeks; 5×/week; Session time and intensity undetermined) C($n=62$) Staying active and in standard hospital care	Mixed exercises are safe, feasible during treatment, and effective in increasing functional capacity and quality of life, and preventing increased fatigue
Travier, N et al. 2015 $n=162$	Breast cancer Chemotherapy	I($n=87$) Aerobic exercise; progressive muscle strength training; major muscle groups; 2 sets of 10 rep (18 weeks; 2×/week; 60 min/session and light intensity) C($n=77$) Usual care	Questionnaire: MFI Exercise reduced fatigue and improved cardiorespiratory fitness and muscle strength. Early exercise intervention is feasible and safe
Van Vulpen, JK et al. 2015 $n=33$	Colon cancer Chemotherapy	I($n=15$) High-intensity interval training; Progressive muscle strength training; 2–10 rep (18 weeks; 2×/week; 60 min/session and moderate intensity) C($n=13$) Usual care	Questionnaire: MFI The program is feasible, safe, and may have beneficial effects on physical fatigue and general fatigue
Waart, H et al. 2015 $n=230$	Breast cancer Chemotherapy	I($n=76$) Mixed exercises; 6 muscle groups; 2 sets of 8 rep (2×/week; 50 min/session with moderate intensity) C($n=77$) usual care without exercise	Questionnaire: MFI The program was safe, feasible, and effective in minimizing the decline in cardiorespiratory fitness and muscle strength
Oechsle K et al. 2014 $n=48$	Hematological diseases Chemotherapy	I($n=24$) Warm up exercise; exercise bike; 3 resistance exercises for major muscle groups (3 weeks; 5×/week; 60 min/session with moderate intensity) C($n=24$) Conventional physiotherapy	Questionnaire: MFI Mixed multimodal exercise has positive effects on physical performance, functionality, and symptom management, especially fatigue, nausea, and vomiting

PIPER, Piper Fatigue Scale; *FACIT-F*, Functional Assessment of Chronic Illness Therapy (FACIT) questionnaire of fatigue; *EORTC QLQ-C30*, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; *MFI*, Multidimensional Fatigue Inventory; *FAS*, Fatigue Assessment Scale; *LASA*, Linear Analog Scale Assessments; *FAQ*, Fatigue Assessment Questionnaire; *FACIT-AN*, Functional Assessment of Chronic Illness Therapy; *PROMIS*, Patient-Reported-Outcomes Measurement Information System; *HIIT*, High Intensity Interval Training; *QoL*, quality of life; *HSTC*, hematopoietic stem cell transplantation

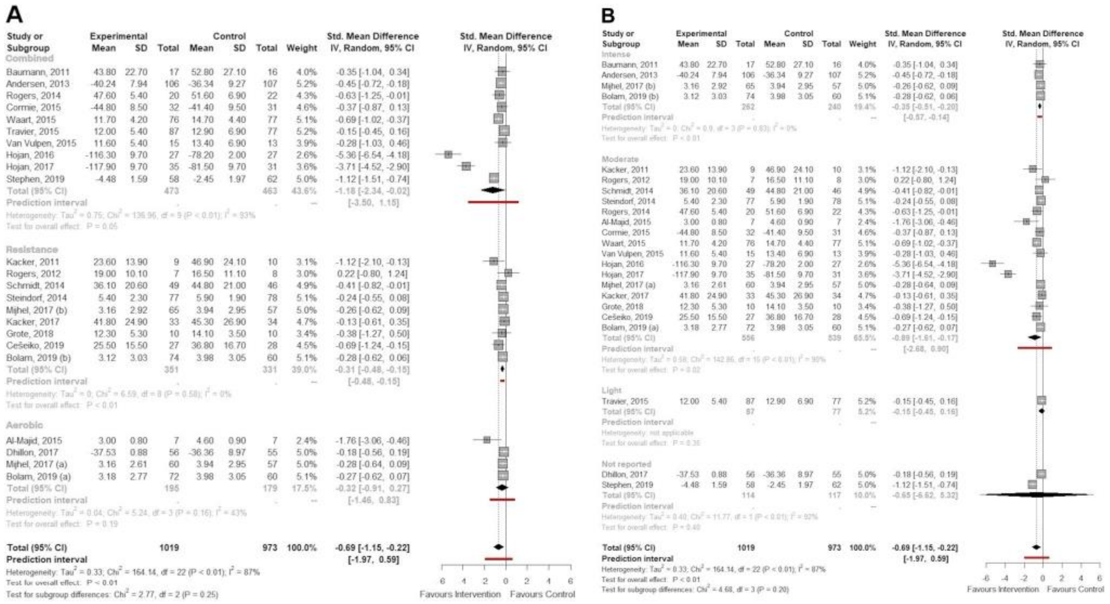

Fig. 2 Effect of different exercise regimens on the manifestation of general fatigue (**A**) and physical fatigue (**B**). Data represent the mean (mean), the standard deviation of the mean (SD), the 95% confidence interval (CI), the sample size by study, and the total of each subanalysis; the weight of the individual study on the final result, the standardized mean difference (SMD), the prediction interval, the heterogeneity between studies (I^2), and the "*p*" value for the determination of probabilistic significance. Exercise effect size was rated as moderate for the relief of general fatigue [SMD = −0.69; 95%CI (−1.15, −0.22)] and physical fatigue [SMD = −0.76; 95%CI (−1.13, −0.39)]

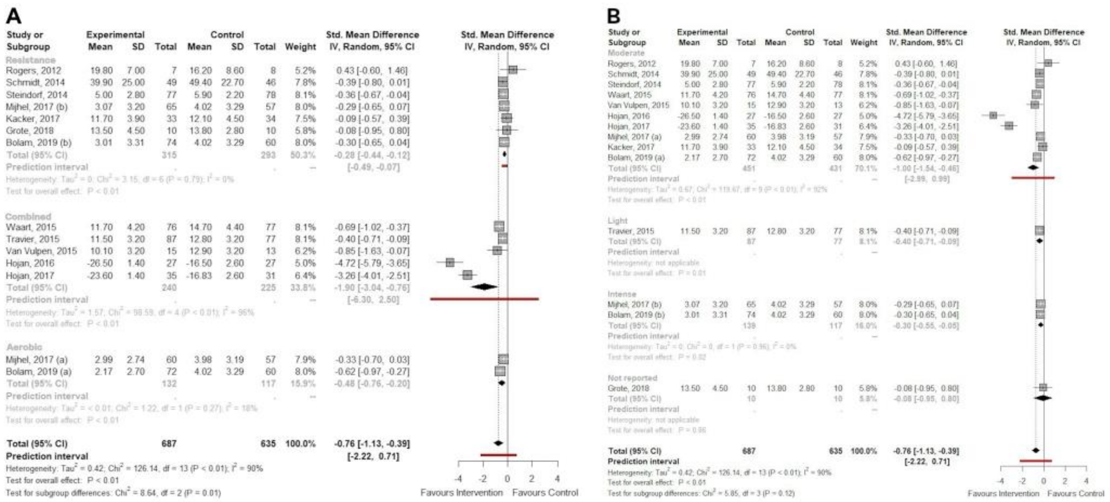

Fig. 3 Effect of different intensities of physical exercise on the manifestation of general fatigue (**A**) and physical fatigue (**B**). Data represent the mean, the standard deviation of the mean (SD), the 95% confidence interval (CI), the sample size per study, and the total of each subanalysis; the weight of the individual study on the final result, the standardized mean difference (SMD), the prediction interval, the heterogeneity between studies (I^2), and the "*p*" value for the determination of probabilistic significance. The effect size of moderate intensity was rated large for the relief of general fatigue [SMD = −0.89; 95%CI (−1.61, −0.17)] and physical fatigue [SMD = −1.00; 95%CI (−1.54, −0.46)]

Most studies used moderate intensity (74%), followed by intense (18%) and light (4%). Figure 3 shows the results of meta-analyses that evaluated the influence of effort intensity on general (Fig. 3A, 23 studies) and physical (Fig. 3B, 14 studies) fatigue. Moderate intensity reduced overall SMD fatigue: −0.89; 95%CI (−1.61, −0.17) $p<0.02$; $I^2=90\%$, and accounted for 65% of the weight in the analysis. Alone, symptom reduction was observed with high intensity physical exercises [SMD=−0.35; 95%CI (−0.51, −0.20) $p<0.01$; $I^2=0\%$], but there was no difference between the different intensities (Chi^2: 4.68, dif=3, $p=0.20$).

The same result was observed in physical fatigue (Fig. 3B), in which the comparison between the subgroups of effort intensities did not reach the cut-off point established for the determination of the statistical difference (Chi^2: 5.85, dif.=3,p =0.12). The highest weight (70%) and effect size also occurred in moderate intensity [SMD=−1.00; 95%CI (−1.54, −0.46) $p<0.01$; $I^2=92\%$]. The intense effort represented 16% of the weight on the overall result and alone contributed to the reduction of the sensation of physical fatigue [SMD=−0.30; 95%CI (−0.55, −0.05) $p<0.02$; $I^2=0\%$].

Meta-regression

The duration of the rehabilitation program and the total number of sessions were related to the size of the intervention's effect on general fatigue. In contrast, the number of weekly sessions and the total number of weeks were the components that contributed most to the relief of physical fatigue (Table 3 - supplementary material). Additionally, a strong tendency for physical fatigue relief was identified with the duration of the physical rehabilitation program.

For each extra week included in the physical rehabilitation program, the effect size is expected to increase on the order of 0.07 for alleviation of general fatigue and 0.09 for physical fatigue. Adding one session per week is expected to increase the relieving effect of physical fatigue by 1.09%. Finally, for each extra session included in the total weeks of the rehabilitation program, an increase of 0.02 in the relieving effect of general fatigue and 0.11 in physical fatigue is expected.

Sensitivity analysis and risk of bias

It was possible to identify in the outcome of general (Fig. 4A) and physical (Fig. 4B) fatigue the discrepancy of the studies by Hojan *et. al.* 2016 and Hojan *et. al.* 2017 [39.40]. By eliminating these two studies from the sensitivity analysis, we observed that for general fatigue there was a significant increase in the prediction interval ($p<0.01$) due to the vast reduction in heterogeneity, which went from 87 to 40%. For physical fatigue, only one study was withdrawn [27], and the interval for estimating the effect of the intervention also increased significantly ($p<0.01$) as a result of the concomitant reduction in heterogeneity, which went from 90 to 25%.

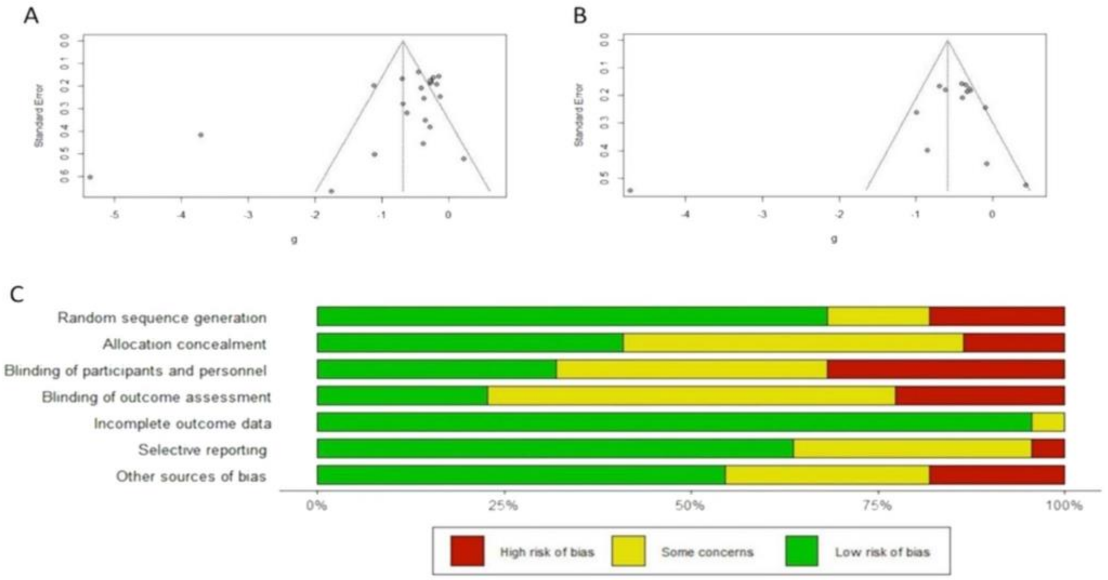

Fig. 4 Sensitivity analysis and risk of bias. Funnel plot for general (**A**) and physical (**B**) fatigue. Risk of bias graph of all studies included in the systematic review

Overall the risk of bias was not low (Fig. 4C). Among the analyzed domains, the blinding of volunteers and researchers who performed the intervention was the one with the worst scores, but the limitations of performing these blindings were considered in the general GRADE composite. Regardless of these considerations, five studies (23%) were classified as having a low risk of bias and 9 (41%) had a high risk. The other studies (36%) left some unclear points regarding the methodology.

Quality of evidence

The evidence was considered moderate for general fatigue, mainly due to methodological issues regarding allocation and evaluation biases (Table 2). For physical fatigue, the evidence was rated as low because, in addition to the biases mentioned above, the number of patients involved was smaller, as was the effect size. The grading of the quality of the evidence was maintained even after the significant reduction in heterogeneity promoted by the removal of the two *outlier studies*.

Discussion

This meta-analysis gathered pertinent information both concerning the effect and the components that structure the physical rehabilitation used for the management of CRF during the acute phase of cytotoxic anticancer treatment. From interventions with different muscle overloads and effort intensities, both general and physical fatigue were reduced. Our results reinforce previous findings that indicate a greater probability of the occurrence of this symptom in patients who remain under the usual care routinely available in the treatment of cancer. It also indicates that combined exercises are more likely to relieve CRF, especially when using moderate intensities. Furthermore, the meta-regression results suggest that both the total number of sessions and the number of weekly sessions can provide additional relief in general and physical fatigue. Similar results have been demonstrated in previous systematic reviews, including patients on anticancer treatment [13] and follow-up survivors [47–49]. In general, it was identified in these studies that the benefits of physical exercise therapy on CRF are independent of the therapeutic moment, as rest is not beneficial for the management of CRF symptoms.

With different types of cancer included, different anticancer protocols were applied. However, it is expected that the triggering of fatigue arises from similar biological mechanisms associated with anemia, hormonal imbalance, cytokine production inflammation, changes in muscle metabolism and reduced ATP synthesis [50, 51].

The variability of some results was considered moderate/high in specific analyses. This implies different conditions between the studies that can be attributed to the type of primary tumor, the antineoplastic therapeutic approach, the characteristics of the physical exercise program and the lack of standardization in the evaluation of fatigue. Presumably, these four aspects exert sufficient weight on the clinical manifestation and measurement of fatigue to the point of overcoming the strategy adopted to match the effect of the intervention through the SMD. In addition, age, sex, and overlapping comorbidities may still play an essential role in the disparity of outcomes [52].

Table 2 Synthesis of the analysis of the quality of evidence based on the GRADE system

Population	Patients undergoing cancer treatment with chemotherapy or radiotherapy or both				
Settings	Clinical trail controlled by randomized control group				
Intervention	Physical rehabilitation with exercise				
Control	Patients undergoing usual care for cancer treatment with chemotherapy or radiotherapy or both				
Outcomes	No. participations(no. reports)	SMD—Hedgs' G Adjusted (95% IC)	I^2	Prediction interval	GRADE
General fatigue	1.992 (23)	−0.69 (−1.15 to −0.22)	87%	−1.97 to 0.59	⊠⊠⊠☐
After sensitivity analysis corrections	1.872 (21)	−0.40 (−0.55 to −0.27)	40%	−0.81 to 0.01	MODERATED[a]
Physical fatigue	1.322 (14)	−0.76 (−1.13 to −0.39)	90%	−2.22 to 0.71	⊠⊠☐☐
After sensitivity analysis corrections	1.268 (13)	−0.42 (−0.58 to −0.27)	25%	−0.73 to −0.11	LOW[a,b]

SMD, standardized mean difference; according to the guide proposed by Colditz GA and Miller JN (1998) [43] for interpreting the magnitude of the SMD in the social sciences: small, SMD = 0.2; medium, SMD = 0.5; and large, SMD = 0.8

[a]Downgrade one level for within-study of bias due to issues relating to the allocation concealment and blind of the outcome assessors for must studies

[b]Downgrade one level for imprecision due to small number of participations

Therefore, this lack of consensus or large variability on the assessment of CRF may explain the technical difficulty involved, especially when treating oncologic patients, who are in multiple overlapping treatments [53]. The misperception about the low disposition may be easily normalized by patients, mainly because scales show important variability and CRF is subjectively assessed on the mental and physical questions, thus creating a barrier to the diagnosis of fatigue [12].

A meta-analysis compared the effect of pharmacological, psychological, and physical rehabilitation treatments on CRF. One hundred thirteen studies were included with a total of 11,525 patients, with half of the sample involved breast cancer exclusively. Exercise and psychological intervention were effective in reducing fatigue during and after cancer treatment and were better compared to available pharmacological options. The effect size of physical exercise on CRF was greater than pharmacological, psychological treatment alone, and psychological treatment combined with exercise [54]. The number of studies analyzed was much higher than ours; however, part of the volunteers included were in a phase of treatment where the acute effects give way to the chronic effects of the anticancer treatment, eventually favoring the performance of the patients in follow-up.

The late symptoms of CRF imply the participation of different mechanisms in the side effects acutely induce by cytotoxic therapy, which are usually associated with the induction of fatigue in an intense and temporary cycle. The results found in the meta-regression point to a significant and inverse relationship between fatigue symptoms and the number of weeks of rehabilitation. This behavior suggests that acute onset fatigue goes through a moment of relief before the later effects are more intense. Subjective analyses such as fatigue are strongly linked to the patient's expectation regarding the prospective clinical evolution, which in the long-term may not manifest. However, the influence of the cumulative effect of physical exercise on the perception of fatigue symptoms cannot be completely ruled out, as the studies included in this review prescribed exercises according to clinical characteristics, which reduces the chances of overtraining [55].

The components of the physical rehabilitation program that characterize aerobic and resistance physical exercises are naturally different. Among the protocols described in the literature, there are many operational nuances, even between structured programs with aerobic exercises. It was observed that there was a predominance of structured protocols with resistance and combined exercises, emphasizing that the results obtained with exclusively resistance exercise were more consistent and practically showed no heterogeneity, indicating greater therapeutic uniformity regardless of the clinical diversity in which they were used.

Although the projection of the probability of the effect of physical therapy on CRF requires caution regarding the variability of the incidence of these symptoms in the initial phase of cytotoxic anticancer treatment, our findings corroborate the study by Brown et al. (2011) [56], who demonstrated that resistance exercise reduced CRF more than aerobic exercise at any level of physical exertion. The 44 studies gathered 3,253 patients undergoing treatment with different types of cancer in both the acute and chronic phases of cytotoxic effects. The authors attributed the relief of CRF to attenuation of the progression of muscle loss and muscle metabolism enhancement adaptations. This relationship explains the more favorable results observed in patients exposed to resistance and combined exercise, since with aerobic exercise alone, there is little development of strength. Presumably, this is the theoretical rationale manifested in clinical practice through reports of relief from the feeling of fatigue, but sufficient objective data to prove this correlation in cancer patients is lacking.

In the secondary analyses carried out, our results support the importance of moderate intensity because in addition to being the most studied in this population, it was the one that promoted more significant relief from general and physical fatigue. The high heterogeneity between the studies limited the precise definition of the most efficient protocol because in addition to the operational differences, it is also necessary to consider the sample heterogeneity. Another limiting factor might be linked to the low number of studies that used high and light intensities. This imbalance denotes a certain consensus among researchers regarding the risk/benefit ratio attributed to the intensity of physical effort. In clinical practice, this can be interpreted as a positive sign toward consensus building. On the other hand, the high relative number of studies that used moderate intensity generates a mathematical distortion, giving greater weight and visibility to the size of the effect of this intensity.

The acceptance and tolerance of effort seem are greater for exercises with moderate intensity, especially in more aggressive clinical situations, where the gain in strength seems to increase self-esteem and vitality [56]. In addition to the influence on fatigue, the authors also report that moderate and intense physical exercises positively influence pain relief, reduction of functional limitation, and subsequent return to work. Compared to aerobic exercise, resistance exercise is generally more intense, brief and potentially better tolerated. The preference for the prescription of moderate intensity resistance exercises may be linked to the expectation that with this muscle overload, there may be an increase in muscle protein synthesis and a reduction in the rate of development of sarcopenia [56–58]. Recently, was demonstrated that lower-intensity exercises have a low effect on the management of CRF [57]. Nonetheless, this statement cannot be supported for the period of cytotoxic treatment, because few clinical trials have tested the exclusive effect of low-intensity exercise.

Despite so many discrepancies between physical rehabilitation programs in the oncological scenario and fatigue assessment tools, there is already some consensus regarding the benefit of exercise for relieving CRF [12, 58]. However, the expected effect size for symptom relief during the acute phase of cytotoxic treatment remains unclear.

Although a comprehensive review of literature regardless of cancer type and patients' clinical stage issue, there remain certain limitations that must be considered when interpreting the results of this study. The patients included were in chemotherapy or radiotherapy, were not in advanced clinical stage, but would can presented contraindications for rehabilitation in this period. Moreover, the ECRs didn't show the chemotherapy moment or the antineoplasic protocols used. Compared with prior systematic reviews who addressed this topic, we performed more detailed subgroup analyses in accordance with rehabilitation intensity and volume. Thus, our conclusions can provide a more meaningful reference for clinical professionals to use in the oncology rehabilitation but the clinical status of the patient needs to be considered daily before starting the physiotherapy session, especially in the presence of chemotherapy protocols that induce myelosuppression or severe cytopenia.

Conclusion

Physical exercise combined with moderate intensity promoted more significant levels of general and physical fatigue relief during the acute phase of cytotoxic treatment. The data indicate that the number of total and weekly sessions contribute to symptom reduction. However, after analyzing the quality of the evidence, it is clear that the probability of replicating these effects is moderate for the treatment of general fatigue and low for physical fatigue, which justifies the continuity of research.

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Author contribution All authors planned the search strategy; Giana Penna, Tassiana da Silva, and Douglas Maquart Otto performed the searches and extracted the data into tables and endnote which were checked by Fabricio Macagnan. Anderson Pedroni synthesised the findings. Giana Penna, Douglas Maquart Otto, and Tassiana da Silva drafted the paper; Fabricio Macagnan and Anderson Pedroni critically revised the work. All authors contributed to the writing and editing of the final draft and have approved the submitted version.

Data availability This study did not generate any new data.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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4 ARTIGO 2 (Será submetido para publicação na revista *Supportive Care in Cancer*)

5 CONCLUSÃO GERAL

O exercício físico é um dos principais recursos da fisioterapia para prevenir e tratar diversas disfunções, não apenas físicas, mas mentais e psicossociais. Os efeitos do tratamento onco-hematológico podem ser amenizados e tratados com este recurso que possui grande potencial, desde que seja devidamente prescrito.

Os pacientes onco-hematológicos mostram-se fragilizados em todos os âmbitos, por isso é essencial demonstrar a segurança da utilização do exercício físico na reabilitação física. Quimioterapias de altas doses não impediram a realização dos protocolos de intervenção. Entretanto, o curto período para aplicação da reabilitação somado ao procedimento do TCTH e todos os seus efeitos colaterais tornaram-se um grande desafio para o incremento da FRC e do desempenho físico. Apesar disso, foi possível prevenir a piora aguda relacionada ao TCTH, mantendo assim os valores da avaliação funcional da admissão hospitalar.

Nossos achados demonstram que mesmo em fases críticas do tratamento antineoplásico citotóxico, o exercício físico com diferentes sobrecargas musculares pode ser implementado tanto para prevenir repercussões agudas do TCTH quanto para melhorar a funcionalidade dos pacientes em outras fases do tratamento.

6 IMPACTOS DO TRABALHO

Cientificamente realizamos os dois tipos de estudo com maior impacto cientifico, uma revisão sistemática, que norteou condutas referente ao atendimento de pacientes em tratamento citotóxico, e posteriormente um ensaio clínico randomizado que conduziu diferentes modos de intervenção na internação para o TCTH. Este estudo apresenta impacto não apenas científico, mas assistencial, pois clinicamente demonstrou ser uma realidade factível para reabilitar pacientes submetidos a tratamentos onco-hematológicos potencialmente agressivos, principalmente aqueles com déficit de funcionalidade, força muscular periférica e queixas de fadiga. Os diferentes modos de reabilitação física podem ser incorporados na assistência sempre correlacionando com medidas de viabilidade clínica e segurança para o paciente. O complexo cenário da onco-hematologia exige raciocínio clínico diário, e o exercício físico é uma estratégia segura e eficaz para manejo de sintomas e repercussões físicas e emocionais em diferentes períodos do tratamento.

Ainda que não tenha sido possível afirmar qual melhor modo de reabilitação para os pacientes em TCTH, foi demonstrado que independente do tipo de exercício, podemos auxiliar para que este paciente tenha alta hospitalar com condições físicas semelhantes à admissão e com grandes possibilidades de retorno às suas atividades de vida diária.