

Therapeutic Education and Physical Activity to Support Self-management of Cancer-related Fatigue in Hematologic Cancer Patients: Protocol of a Feasibility Randomized Controlled Trial

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Abstract

Introduction: Hematologic malignancies account for nearly 8% of new cancer diagnosis in Italy. Cancer-related fatigue (CRF) is one of the most distressing symptoms reported by patients with cancer. As CRF has a multifactorial etiology, physical activity and therapeutic education may be beneficial for managing CRF, both during and after cancer treatment. However, there is a lack of evidence specific to hematologic malignancies. This paper describes the protocol of a feasibility study on Therapeutic Education and Physical Activity (TEPA) intervention to support self-management of CRF in patients with hematologic malignancies. **Methods:** TEPA was addressed to newly diagnosed adult individuals with hematologic malignancy able to take part in a rehabilitation programme at the AUSL-IRCCS of Reggio Emilia. The protocol was developed in 2 phases. Phase I was an observational cohort study involving a convenience sample of 10 participants with the aim to evaluate the feasibility of the assessment schedule and to register longitudinal clinical data regarding CRF (FACIT-F), psychologic distress (NCCN Distress Thermometer), QoL (EORTC QLQ-C30), physical performance (TUG and 6MWT) and habitual level of physical activity during first months after diagnosis. Phase II (underway) is a feasibility randomized controlled trial (TEPA) involving a convenience sample of 40 participants and comparing 2 parallel active interventions (Therapeutic Education versus Therapeutic Education and Physical Activity) on top of usual care. The primary aim is to estimate the feasibility of TEPA, measured by the adherence rate to the intervention. Secondary aims are: to estimate the effect size of TEPA in terms of changes in CRF, psychological distress, QoL, physical performance and habitual level of physical activity (measured as in Phase I); to collect patient satisfaction, perception of usefulness of the TEPA intervention and data on long-term adherence to an active lifestyle. Data are collected in both phases at the time of diagnosis and then at 1-, 3- (completion of intervention) and 7-month follow-up. **Discussion:** Data on feasibility and effect size of TEPA will be analyzed upon completion of Phase II, allowing us to design a large, adequately powered RCT to verify the effectiveness of this intervention on CRF management in patients with hematologic cancer. Trial registration: clinicaltrials.gov; Trial registration number: NCT03403075

Keywords

cancer-related fatigue, physical activity, therapeutic education, hematologic malignancies, patients with cancer, nonpharmacological treatments, rehabilitation, self-management, physical therapy.

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Introduction

Cancer is the second cause of death in Italy, the first being cardiovascular diseases. While cancer incidence is increasing, survival is as well, thanks to early diagnosis and effective therapies. Hematologic malignancies account for nearly 8% of new cancer diagnoses in Italy¹ and represent a heterogeneous group of diseases with differing clinical courses.

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Moreover, the treatment of hematologic malignancies varies based on the type and stage and can consist of radiotherapy, chemotherapy, immunotherapy and/or autologous or allogeneic stem cell transplantation,² all of which can cause long-term side effects, such as physical deconditioning, worsening of cancer-related fatigue (CRF) and of quality of life (QoL).

Cancer-related fatigue (CRF) has been defined as “a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment which is not proportional to recent activity and interferes with usual functioning.”³ CRF has a multifactorial etiology and affects 60% to 90% of hematologic cancer patients,⁴ representing one of the most distressing symptoms reported by patients with cancer. Further, it can persist long after the end of treatment, leading to a worsening of QoL and to physical disability. Beyond potentiating comorbidities that can amplify CRF, such as anemia, neutropenia, sarcopenia, etc.,⁵ it has been hypothesized that the mechanism underlying CRF is the vicious circle of fatigue, limitations on activity and physical deconditioning, which in turn increase fatigue.⁶ This vicious circle results in physically deconditioned individuals who are no longer able to carry out their usual activities and who also have a worse response to cancer treatment.³

Physical deconditioning is highly prevalent in individuals with hematologic malignancies; it derives both from some specific side effects of treatment, such as cardiotoxicity, neurotoxicity or cachexia and from the widespread belief that the patient should rest.² Both clinicians and patients tend to view CRF as an inevitable consequence of illness.⁵ Moreover the prevailing advice for patients is to rest and avoid physical activity in order to face CRF, even if recent Cochrane review suggests that physical exercise, as a nonpharmacological treatment, added to standard care might improve fatigue and depression.⁴ Therefore, an additional challenge when treating individuals with hematologic malignancies should be to avoid physical deconditioning, thereby lessening associated CRF.

Still, several nonpharmacological treatments have been suggested for CRF: cognitive behavioral interventions, physical activity, relaxation techniques and therapeutic education.⁷ Of these, physical activity seems to be particularly promising as it counteracts physical deconditioning, thereby interrupting the above-mentioned vicious circle. Physical activity is both safe and recommended at any cancer stage because it improves physical functioning, CRF, QoL and psychosocial well-being.⁸ As for how much physical activity to perform, patients should be “as physically active as their abilities and conditions allow”⁸ and they should avoid inactivity: “some physical activity is better than none.”⁸ A recent comprehensive review highlighted the positive effects of physical activity on fatigue and depression in patients with hematologic malignancies; aerobic exercise in particular

seems to improve the oxygen system and to increase cardio-respiratory fitness, muscle strength and physical well-being⁴ in this population. Nevertheless, the information patients receive on physical activity during the course of cancer is often vague,⁹ and patients lack individualized support regarding the recommended physical activity during treatment.¹⁰

Concerning therapeutic education interventions, several studies suggest that they may be particularly useful to cancer survivors in managing CRF as an adjunct to exercise programmes, both during and after treatment.¹⁰⁻¹² Although these interventions seem effective when delivered, whether verbally or in writing, by a licensed professional or a trained nonprofessional both to individuals and to groups, future research should identify the most appropriate contents and the most effective delivery modalities to address CRF.¹¹

A recent review supports the implementation of brief, focused multidimensional rehabilitation programmes combining physical activity and therapeutic education for cancer survivors.¹⁰ Therapeutic education usually consists of educational group sessions led by physical therapists (or other trained professionals) that focus on relevant cancer-related topics, such as fatigue, pain, sleep, emotional changes and physical exercise, and that are supported by written material.¹⁰

To date, the effectiveness of these multidimensional rehabilitation programmes has been studied in populations with different cancer diagnoses, though few studies have examined individuals with hematologic malignancies.¹⁰ Given the characteristics of hematologic malignancies, which also affect young individuals and which require multiple treatments that result in fatigue, we believe it is time to collect evidence on the effectiveness of multidimensional rehabilitation in this population.

We therefore implemented the TEPA (Therapeutic Education and Physical Activity) intervention, a multidimensional rehabilitation programme targeting the needs of patients with hematologic malignancies. The feasibility and the impact of the TEPA intervention are being verified through a randomized controlled trial (RCT).

In this manuscript we report the RCT protocol and describe the TEPA intervention in detail to allow for its generalization.

Methods

This study protocol is reported according to the SPIRIT Checklist.¹³ It describes a single-center clinical trial that was developed in 2 phases: Phase I was an observational study, Phase II (underway) a pilot feasibility RCT. The entire project took place at the Santa Maria Nuova Hospital (SMN), Azienda Unità Sanitaria Locale-IRCCS of Reggio Emilia, Italy.

The study was approved by Provincial Ethics Committee of Reggio Emilia on July 19, 2017 and registered on ClinicalTrials.gov (NCT03403075).

Table 1. Assessment Schedule.

	T0	T1	T2	T3
Assessment/Outcomes	Between diagnosis and beginning of life-saving treatments	1 mo after T0	3 mo after T0	7 mo after T0
FACIT-F: Perception of CRF	X	X	X	X
NCCN Distress Thermometer: distress rate and problem checklist	X	X	X	X
EORTC QLQ-C30: Quality of life	X	X	X	X
TUG: mobility, balance, walking ability and fall risk	X	X	X	X
6MWT: functional exercise capacity ¹⁵	X			X
Quality and amount of physical activity	X			X
Blood chemistry tests ^a	X	X	X	X
Participant satisfaction and perception of usefulness ^b				X
Adherence to an active lifestyle and the amount of physical activity performed ^b				X

^aThe most recent blood chemistry tests were collected at each assessment time.

^bPhase II only.

Participants

For both phases, adult patients (≥ 18 years) referred to the Hematology Unit of the SMN were screened for eligibility by staff hematologists and physical therapists. Patients were included if affected by a first or an early relapse of hematologic malignancy and candidate to chemotherapy and/or radiotherapy. Exclusion criteria were (a) poor prognosis (< 12 months) and (b) clinical condition that may hinder participation in the rehabilitation programme (eg, dementia, psychiatric pathology, blindness, deafness, language barriers, communicative deficits, etc.). Eligible patients were fully informed about the aims and methods of the study and written consent was collected by the physical therapists.

Objectives

The primary aim of Phase I was to evaluate the feasibility of the assessment schedule and to register longitudinal clinical data regarding CRF, psychologic distress and other relevant problems, QoL, physical performance, habitual level of physical activity and other clinical characteristics in a cohort of patients with hematologic malignancies. These data were collected in order to learn more about the natural trend of these parameters during the course of curative care of patients with hematologic cancer who did not undergo any specific intervention to relieve symptoms, avoid physical deconditioning and/or maintain QoL.

The primary aim of Phase II is to investigate the feasibility of TEPA intervention in patients with hematologic cancer.

Secondary aims are:

- to estimate the effect size of TEPA intervention in terms of changes in:

- cancer-related fatigue (primary clinical outcome)
 - psychological distress, QoL, physical performance and habitual level of physical activity
- to estimate the impact of TEPA intervention on:
 - patient satisfaction and perception of usefulness of the intervention provided¹⁴
 - long-term adherence to an active lifestyle¹⁴

Phase I

Phase I was an observational cohort study which took place from September 2017 to February 2018 on a convenience sample of 10 participants. Data were collected prospectively from time of diagnosis (T0) up to 6 months from the beginning of treatment (T3) by specifically trained physical therapists, according to the assessment schedule described in Table 1.

Furthermore, data on socio-demographics and type of hematologic malignancy were collected at T0. A brief summary of Phase I results is presented in Supplemental Appendix 3.

Phase II

Phase II is a pilot RCT comparing 2 parallel active interventions delivered on top of usual care. The aim of this pilot RCT is to assess the feasibility of the TEPA intervention and estimate its impact on clinically relevant outcomes (particularly regarding CRF) in a convenience sample of 40 participants. In order to assess the feasibility of the TEPA intervention we will compare the number of sessions completed to those planned for each participant. To estimate the effect size of TEPA intervention, patients included in Phase II follow the same assessment schedule as that for Phase I (Table 1), including socio-demographic and clinical data

collection. Furthermore, we will administer a questionnaire at T3 to collect information on participant satisfaction and perception of usefulness of the programme provided, the participants' adherence to an active lifestyle and the amount of physical activity performed at that point.

Randomization

After the first blinded assessment (T0), patients are randomized into Therapeutic Education (TE) group or Therapeutic Education and Physical Activity (TEPA) group, in a 1:1 allocation ratio. The Clinical Trial and Statistics Unit of the Azienda Unità Sanitaria Locale-IRCCS of Reggio Emilia generated the randomization sequence and notified the researchers of group allocation by telephone to ensure allocation concealment.

TEPA Interventions

The TEPA interventions (TE and TEPA) were developed in 2017 by a multiprofessional research team that included physiatrists, hematologists, physical therapists and nurses. Both are administered between T1 and T2 on top of usual care, intended as the treatment regimen set by the referring haematologist:

- the TE group receives 2 educational group sessions led by 2 trained physical therapists, held in the hospital and open to caregivers as well. Each session lasts about 1 hour and is administered to small groups from 2 to 6 participants (min-max). The 2 sessions share a common structure but address specific topics: CRF in session 1 and physical activity in session 2 (Table 2a). The 2 sessions are not delivered in any specific order, so each participant could start with either. The topics are addressed through various modalities (eg, oral presentations, brainstorming, group discussion, simulations, etc.) with the support of a multimedia interactive whiteboard and a projector. Participants are also provided with a leaflet summarizing the key concepts addressed during sessions.
- The TEPA group receives 6 individual sessions with a physical therapist as well as the 2 group sessions as the TE group attended. Individual sessions are scheduled once a week or every 2 weeks and held at the hospital. Each lasts about 20 minutes; the objectives are to discuss the topics addressed in the group sessions more in depth and to set a personalized weekly physical activity programme (Table 2b). The physical activity programme, called the Activity Plan (Supplemental Appendix 1), is based on each participant's clinical condition and preferences and is performed independently. During the individual

sessions, the physical therapist assists the participants in planning their Activity Plan of the following week/s. Starting with session 2, and then at every other session after that, the participant's adherence to the Activity Plan is checked. The physical therapist then assists the participants in trying to increase the physical activity level of their subsequent Activity Plan; if the Activity Plan is not successful, participants are assisted in applying problem-solving strategies to plan an achievable physical activity level. Furthermore, patients are provided with a leaflet that summarizes the key concepts addressed during the individual sessions, lists the suggested exercises and includes the activity diary (Supplemental Appendix 2) to register the physical activity to be performed independently, per the Activity Plan.

Contents

The setting and the delivery modalities of both active interventions are based on the Stanford Chronic Disease Self-Management Program (CDSMP),^{16,17} which has been implemented in Italy for post-acute stroke survivors,¹⁸ as well as on previous findings observed in patients with CRF.^{19,20} The data registered in Phase I confirmed the need to receive information on CRF's management in this population.

The contents of the group sessions are inspired by Macmillan Cancer Support experiences, in particular by the web-based RESTORE tool, which is designed to increase self-efficacy in managing CRF.^{12,19}

The contents of the individual sessions are adapted to hematologic cancer patients: participants are provided with useful information on communication strategies, goal setting and problem solving, the role of physical activity in the management of one's own clinical condition, the recognition and management of symptoms due to the disease and its treatments and the management of aids/orthoses. Moreover, according to international recommendations on physical activity,⁸ the importance of maintaining an active lifestyle (ie, 150 minute/week of moderate-intensity aerobic exercise) is stressed. Patients are even encouraged to stay active during oncological treatments, whenever possible.

Statistical Analysis

Data are collected electronically from the Azienda Unità Sanitaria Locale-IRCCS Reggio Emilia database in anonymously and aggregated modalities. Statistical analyzes will be performed using R and SAS.

In the event of withdrawal of informed consent, worsening clinical condition, inability to attend sessions or death, the participant will withdraw from the study.

Table 2. Activities, Aims and Contents of TEPA Intervention.

(a) Group sessions				
Session 1	Activities	Aims	Modalities	Self-management skills practiced and behavior changing techniques used
Session 1 Contents	Presentation of agenda and participants	Promote group socialization	Oral presentation and group involvement	
	Explanation of goal setting and problem-solving strategies	How to plan short- and long-term goals	Oral presentation	Goal setting
	Relaxation activity and diaphragmatic breathing techniques	How to solve problems in case of unsuccessful breathing	Guided imagination	Problem solving Behavioral rehearsal/practice Reducing negative emotions Distraction
	Physical Activity (PA)	How to keep active during and after medical treatments How to set the goal of 150 min/wk of moderate-intensity aerobic exercise in order to maintain healthy lifestyle How to quantify the intensity of the exercise Explain the different kinds of PA (aerobic, strength, flexibility and balance exercise) How to do PA safely	Oral presentation, brainstorming and exercise simulation	Information about health consequences Activity planning and goal setting
Session 2 Contents	Aids and Orthoses	Explain their differences and the purpose of aids and orthoses	Oral presentation	Skill mastery Self-monitoring of outcome of behavior
	Activities	Aims	Modalities	Information about health consequences
	Presentation of agenda and participants	Promote group socialization	Oral presentation and group involvement	Self-management skills practiced and behavior changing techniques used
	Explanation of goal setting and problem-solving strategies	How to plan short- and long-term goals	Oral presentation	Goal setting
	Relaxation activity and diaphragmatic breathing techniques	How to solve problems in case of unsuccessful breathing	Guided imagination	Problem solving Behavioral rehearsal/practice Reducing negative emotions Distraction
	Cancer-related fatigue (CRF)	Give definition of CRF Explain its characteristics and causes	Oral presentation and brainstorming	Information about health consequences Interpretation of symptoms to enhance self-efficacy
	Good communication	Discuss how to manage it Advice on how to ask for help	Oral presentation and brainstorming and group discussion	Social support Instruction on how to perform the behavior Skill mastery
		Training on words that help communication		Behavioral rehearsal/practice Social persuasion

(continued)

Table 2. (continued)

(b) Individual sessions				Self-management skills practiced and behavior changing techniques used	
Session 1	Activities	Aims	Tools		
Session 1	Contents	Make an Activity Plan	Make weekly Activity Plan based on what the person wants to do Choose exercises in the leaflet, as needed	Oral presentation and collaborative goal setting between patient and researcher	Action Planning Skill mastery
		Problem-solving	Explain problem-solving strategies and apply if the previous Activity Plan was unsuccessful (not in the first session)	Oral presentation and collaborative goal setting between patient and researcher	Problem-solving/coping planning
		Check previous Activity Plan	Verify the success of the last Activity Plan by checking the activity diary	Oral presentation	Self-monitoring of Activity Plan result
		Self-management	Explain principle of self-management and vicious circle of symptoms and disabilities	Oral presentation	Enhance knowledge to favour decision making
Session 2		Physical activity (PA)	Repeat and discuss more in depth the concepts explained in group session	Oral presentation	Instruction on how to perform the behavior Information on health consequences Interpretation of symptoms to enhance self-efficacy
	Contents	Goal setting	How to set a PA goal	Oral presentation	Goal setting
		Activities	Aims	Tools	Self-management skills practiced and behavior changing techniques used
	Contents	Make an Activity Plan	Make weekly Activity Plan based on what the person wants to do Choose exercises in the leaflet, as needed	Oral presentation and collaborative goal setting between patient and researcher	Action Planning Skill mastery
		Problem-solving	Explain problem-solving strategies and apply if the previous Activity Plan was unsuccessful (not in the first session)	Oral presentation and collaborative goal setting between patient and researcher	Problem-solving/coping planning
		Check previous Activity Plan	Verify the success of the last Activity Plan by checking the activity diary	Oral presentation	Self-monitoring of Activity Plan result
		Cancer-related fatigue (CRF)	Repeat and discuss more in depth the concepts explained in group session	Oral presentation	Information about health consequences Interpretation of symptoms to enhance self-efficacy

Clinical and demographic data will be expressed in terms of frequency and percentage for categorical variables, mean \pm standard deviation for symmetric quantitative variables, median and interquartile range for skewed ones.

Regarding the primary aim of Phase II (feasibility of TEPA), proportion estimates will be accompanied by Wilson confidence intervals.

As for secondary aims, a confidence interval assuming a normal distribution of the estimator will be provided for both the point estimates (of variations) in single groups and for group comparisons/differences in mean variations of clinical outcomes.

For each problem listed by patients, the proportion estimate in each group will be accompanied by Wilson confidence interval, while group comparisons will be assessed by estimating the OR and its Wald confidence interval.

Finally, adherence to an active lifestyle and level of satisfaction and perception of usefulness of the provided intervention will be described; central tendencies measures will be accompanied by asymptotically valid confidence intervals.

All confidence intervals will be two-tailed and calculated considering a 0.95 confidence level.

All the analyzes will be intention-to-treat and the last available data will be used in case of missing data.

A secondary per-protocol analysis will be planned a priori if adherence does not reach the cut-off of 80%.

Discussion

In this study we describe a multidimensional rehabilitation programme that combines TE and physical activity in an intervention targeting the most frequently reported needs of patients with hematologic malignancies, mainly CRF management and prevention of physical deconditioning.^{21,22} If this intervention, the results of which will be analyzed upon completion of Phase II, proves feasible and useful, this detailed description will allow for its generalization to similar contexts.

To date, a certain degree of evidence supports the effectiveness of brief, focused multidimensional rehabilitation programmes for cancer survivors.¹⁰ Psychosocial interventions, which may include therapeutic education, coping strategy training and/or behavioral interventions, for example, have been proposed to manage CRF in cancer patients.¹¹ Moreover, it has been established that some amounts of aerobic or resistance exercise, or both, could improve cancer-related health outcomes, for example mood disturbances, fatigue, physical functioning and/or health-related quality of life.⁸ In particular, it seems that aerobic exercise might improve CRF and depression in adult patients with hematologic malignancies.⁴ The physical activity interventions tested are usually heterogeneous in terms of type, intensity, duration and frequency of exercise, as is the timing of administration with respect to the patient's clinical pathway.

Generally speaking, physical activity is usually implemented after the completion of treatment or transplant²³⁻²⁸; just a few types of physical activity have been tested during medical treatment.^{21,29} Also, the experimental exercise interventions reported in the literature generally lasts a minimum of 3 weeks and up to 36 weeks, and most interventions consists of a combination of aerobic, strengthening/resistance and flexibility exercises.^{21,22,24,27-34} These interventions are tailored to the patient's capacity and are administered under the supervision or with the counseling of a trained professional, usually a physical therapist. Depending on the cancer stage, interventions take place in the inpatient, outpatient or home-based setting. In most cases, physical activity is tested as a stand-alone intervention, while a few studies associate it with group counseling sessions.^{26,34}

The Phase I data confirmed the feasibility of assessments schedule and the opportunity to involve hematologic cancer patients in an educational intervention in order to allow a better CRF management in the first months after diagnosis (see Supplemental Appendix 3).

The TEPA intervention is novel in 2 ways: first, it has both physical and educational components. Second, it is proposed in the very early phase of the clinical pathway of patients with hematologic cancer to support them in self-managing CRF to prevent physical deconditioning and to alleviate other major symptoms. This experimental intervention encourages participants to engage in 150 minutes of moderate-intensity aerobic physical activity per week, following specific recommendations for healthy lifestyle.⁸ Furthermore, in line with existing indications and programmes on aerobic and resistance training, the TEPA intervention conveys to participants the importance of setting appropriate physical activity goals that balance international recommendations with each patient's clinical condition and preferences. A further novelty is that we assess the impact of TEPA on relevant outcomes weeks after stopping the experimental treatment, allowing us to determine whether any benefit is maintained over time.

It should be noted that the effects of several nonpharmacological interventions to manage CRF have been studied in different cancer survivor groups but have yielded inconsistent results, particularly for patients with hematologic cancer.¹¹ This study will contribute data on the impact of a nonpharmacological intervention addressing the specific needs of this population from the very early phase of the clinical pathway, and it will verify the feasibility of the intervention described. This will allow us to design a large, adequately powered RCT to verify the effectiveness of TEPA intervention on CRF management in patients with hematologic cancer.

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Author Contributions

As dictated by the Authorship guidelines of the International Committee of Medical Journal Editors, all the authors of this manuscript gave substantial contributions to the conception or design of the work or to the acquisition, analysis, or interpretation of data for the work; AND gave substantial contributions to the drafting the work or to its critical revision for important intellectual content; AND approved the final version to be published. All the authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This manuscript was completely written by its authors and reviewed in kind contribution for English language by an editor. The authors did not make use of medical writers.

Declaration of Conflicting Interests

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Research ethics

This independent study was approved by Provincial Ethics Committee of Reggio Emilia on July 19, 2017, and registered on ClinicalTrials.com (NCT03403075).

Dissemination Policy

The authors pursue the publication of this study protocol and its results in terms of feasibility and impact of the TEPA intervention through publication in international scientific journals.

Confidentiality

The demographic and clinical data collected to support the findings of this study are restricted by Ethics Committee of the Vast Northern Emilia (Italy) in order to protect patient privacy. The

data will be available from the corresponding author (Monica Denti PT), upon reasonable request, with the permission of Azienda Unità Sanitaria Locale-IRCCS Reggio Emilia, Italy.

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Supplemental Material

Supplemental material for this article is available online.

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