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REVIEW

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Exercise program for children and adolescents with leukemia and lymphoma during treatment: A comprehensive review

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Abstract

An exercise program (EP) during cancer treatment seems to be a valid strategy against physiological and quality-of-life impairments, but scientific evidence of benefits among pediatric patients is still limited. This review summarizes the literature focused on randomized controlled trials of EP offered to patients during leukemia and lymphoma treatment. Studies published up to June 2017 were selected from multiple databases and assessed by three independent reviewers for methodological validity. The review identified eight studies, but several types of bias have to be avoided to provide evidence-based recommendations accessible to patients, families, and professionals.

KEYWORDS

exercise program, neurotoxicity of therapies, pediatric oncology, supportive care

1 | INTRODUCTION

High-dose chemotherapy is the treatment strategy for most common childhood acute leukemia and lymphoma. Cyclophosphamide, methotrexate (MTX), vincristine (VCR), and other chemotherapeutic agents are responsible for several side effects on cognitive, neurological, and motor functions, which negatively impact patients' development. Patients with leukemia and lymphoma are at risk for developing complications such as decreases in muscular strength, impaired gross and fine motor skills, osteonecrosis, and fatigue.[1,2] These outcomes are evident at diagnosis and especially at an early stage of treatment.[3] A study by Akyay et al.[4] highlighted that endurance, strength, and functional mobility were poorer at the end of the induction phase compared with the period of the diagnosis. Symptoms such as fatigue, low aerobic capacity, and lack of strength might persist after patients' complete treatment and lead survivors to be less active and at greater risk of obesity than their healthy peers.[5,6] For instance, due to high doses of VCR and MTX, low exercise capacity is expected in leukemia survivors.[7] Moreover, muscle weakness and reduced mobility are always followed by a poor health-related quality of life (HRQoL) and poor self-esteem and self-efficacy.[3]

Physical activity is a key factor in the development of healthy children and has been suggested to improve cardiovascular capacity, strength, and daily functioning in a wide range of pediatric chronic diseases (e.g., juvenile idiopathic arthritis, cerebral palsy, and cystic fibrosis).[8] In healthy populations, research indicates that physical inactivity is an independent risk factor for noncommunicable diseases such as obesity, diabetes, cardiovascular disease, and cancer.[8] Promoting physical activity in childhood cancer patients and survivors is important, as they are at a greater risk (compared to healthy children) of developing a sedentary lifestyle and the associated comorbid conditions. Published literature now supports the contention that participation in an early individualized exercise program (EP) for patients with cancer prevents or reduces some severe sequelae and muscle toxicity.[9] However, exercise benefits among cancer children and adolescents continue to be underestimated.[10–12]

A recent review by Braam et al.[13] considered six studies (both randomized controlled trials [RCTs] and controlled clinical trials) on EP among children and adolescents with cancer on and off treatment. The review highlighted that some questions regarding exercise benefits have remained open. First, very few RCTs of EP with young cancer population have been carried out. RCTs are the most rigorous methods to determine whether a cause–effect relationship exists between an intervention and an outcome. The paucity of these types of studies plus the small sample size did not allow researchers to provide any solid evidence. Also, the specific features of these studies are still to

Abbreviations: ALL, acute lymphoblastic leukemia; EP, exercise program; HRQoL, health-related quality of life; MTX, methotrexate; RCTs, randomized controlled trials; VCR, vincristine

be determined (e.g., timing and intensity). Braam et al.'s review has proved very useful even if it does not limit its attention only to the study of RCTs among patients with leukemia and lymphoma during treatment. To date, there seems to be a lack of systematic reviews that analyze the effect of RCTs on children and adolescents with leukemia and lymphoma during treatment. It is important, as these patients form the largest category of children and adolescents with oncological diagnoses.[14] Furthermore, patients with hematological cancer typically present more strength deficit or chemotherapy-induced peripheral neuropathy side effects than patients with other types of cancer such as brain or bone tumors.[15] So, similar characteristics among children and adolescents with leukemia and lymphoma make them a homogenous group to create unique EP recommendations and their rate of diagnosis permits enrollment of a large sample of patients. As these patients have the highest survival rates and major late effects, surveillance programs are recommended. Thus, concentrating on patients undergoing treatment would allow the creation of an EP with a prevention perspective by limiting several treatment late side effects.

Therefore, the main aim of this review is to summarize and describe RCTs of EP carried out on children and adolescents with leukemia and lymphoma during treatment, providing healthcare professionals with a practical vision to enable them to recommend exercise to their patients.

The secondary objective is to discuss their major biases and deficiencies to propose valid insights for future trials with children and adolescents.

2 | METHODS

2.1 | Eligibility criteria

This review only included RCTs of EP conducted with a control group undergoing standard care.

Inclusion criteria were as follows: (1) RCT articles published until June 2017, (2) patients with leukemia or lymphoma aged 0–18 years, (3) EP offered within the cancer treatment protocol (also considering the maintenance phase), and (4) articles focused on the effect of EP on physical and/or psychosocial functions.

2.2 | Data source and search strategy

Six biomedical databases were used as follows: PubMed, The Cochrane Library, CINAHL, Scopus, PEDro, and PsycInfo. Manual searches were also performed and further papers were found. To compile the research array, the primary search terms "Leukemia" and "Lymphoma" were combined with "Physical Exercise" and "Rehabilitation" (MeSH terms or free-text words). Some examples of full search strategies were as follows: "Lymphoma AND Motor Exercise," limit: clinical trial and age range 0–18 years (Figure 1).

2.3 | Study selection

The full texts of articles that seemed to meet the inclusion criteria were retrieved for further evaluation according to predefined criteria.

2.4 | Data extraction

Eight studies met the inclusion criteria. After the search strategy, two reviewers (G.Z. and F.R.) independently identified studies meeting the inclusion criteria. Both authors resolved discrepancies by reaching a consensus. In two cases, a third reviewer (C.C.V.) was needed; we sought another opinion of the studies by Courneya et al. [16] and Kauhanen et al.[17]; Courneya et al.'s study was then excluded[16] because the EP considered patients who were 18 years or older; and even though the study results are ongoing, the Kauhanen et al.'s study was included.[17]

The following data were extracted from each study: references, method and design, sample, EP, control group program, outcomes and possible adverse effects, evaluation tools, effects of EP on outcomes, gaps, bias, and requirement (Supplementary Table S1).

3 | SELECTED STUDIES ANALYSIS

A total of 31 papers were identified from the database and manual search. Twenty-two manuscripts were excluded after evaluating the abstract as they did not fit the search criteria and one was excluded by consensus of researchers.[16] Therefore, eight papers were included in this review (Figure 1).

3.1 | Method and design

The randomization process was adequately specified in five studies[17–21] and in three studies it remained unclear.[22–24] Four studies included patients during the maintenance phase[18,22–24]: two studies indicated the timing as "after diagnosis"[17,21] and in two studies the treatment phase was not specified.[19,20] Two studies measured pre- and post-EP,[18,24] four studies considered different measurements during EP,[19,20,22,23] and two studies had only a follow-up measurement.[17–21]

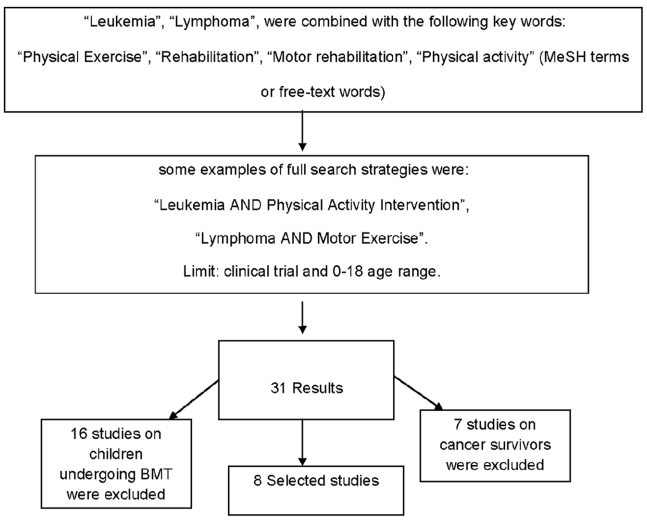

FIGURE 1 Literature regarding RCTs for children and adolescents with leukemia and lymphoma during treatment

3.2 | Sample

The sample size given in two studies was 14 patients[22,23]; other studies had samples of 28,[18] 29,[19] 34,[17] 41,[23] 51,[21] and 68 patients.[20] Most studies included participants aged 3–18 years[17–20,22–24] and only one study included patients aged 1–18 years.[21] Five studies were carried out with a sample taken exclusively from acute lymphoblastic leukemia (ALL) patients[18,23,24]; one study included children with ALL and other types of cancer outside the central nervous system (such as lymphoma),[17] another study considered solid tumors or acute myeloid leukemia,[19] and one study considered patients with any type of childhood malignancy.[20]

3.3 | Exclusion criteria

All the studies, except for one,[22] highlighted the exclusion criteria.

3.4 | Exercise program

Five studies included both supervised hospital-based programs and home-based EPs,[17–19,21,24] while home-based EPs were prescribed in two studies.[22,23] The duration of the studies varied from less than 1 month[19] up to 2 years.[21] The EP was based on aerobic training in most studies.[17–19,22] Strength training was performed in three studies[18,21,24] and two studies prescribed stretching exercises.[18,21] One study[23] used a threshold device. Another study proposed combined EP training with a combination of cardiorespiratory and strength exercises with psychosocial activities consisting of psychoeducation and cognitive behavioral techniques.[20]

3.5 | Control group program

In seven studies, children in the control group had to follow care as usual.[18–24] In one study, the control group received the general recommendation to do 30 min of exercise per day.[17]

3.6 | Outcomes and possible adverse effects

Regarding the outcome measures, three studies examined cardiorespiratory fitness[18,22–24] while four examined flexibility.[18,21,22,24] Three studies measured muscle endurance[19,22,23] and one study examined strength.[18] Two studies examined functional mobility[18,19] and two studies examined motor performance.[17,21] Three studies analyzed anthropometric factors[17,21,22] and included variables such as body composition and bone mineral density.[21]

Two studies examined the amount of physical activity and sedentary behavior.[17,22] Three studies examined fatigue[17,19,20] and three studies examined HRQoL.[18–20] Only one study examined psychosocial outcomes such as behavioral problems, depressive symptoms, and self-perception variables.[20]

Other outcome variables studied were as follows: the feasibility of an EP intervention,[19] adherence to exercise,[18] the children's perceptions of the activities,[17] sleep efficiency,[19] food intake,[22] and the child's thoughts about disease.[24]

3.7 | Evaluation tools

The "9 Min Run-Walk Test"[18,22–24] and the "Progressive Aerobic Cardiovascular Endurance Run (PACER)"[22] examined cardiorespiratory fitness. Goniometer and the "Sit It and Reach Test"[22] examined flexibility. "Push up Test,"[22] "Digital Manometer,"[23] and "Dynamometer"[24] examined muscle endurance. The "Hand-Held Dynamometer" measured strength[18] and the "Timed Up And Down Stairs Test" measured functional mobility.[18,24] The "Dutch Bayley Scales of Infant Development" and the "Movement Assessment Battery for Children"[17,21] examined motor performance. Anthropometric factors were examined using body mass index, muscle mass, weight and height measures, and a dual energy X-ray absorptiometry.[17,21,22] The amount of physical activity and sedentary behavior was analyzed through two questionnaires and a diary proposed by the authors.[17] The "PedsQL Multidimensional Fatigue Scale" and the "Fatigue Scale for Children with Cancer" examined fatigue.[17,19,20,25] "PedsQL 4.0 Generic Core Scale"[26] and the "PedsQL 3.0 Cancer module"[27] examined HRQoL. The "Child Behaviour Checklist (CBCL)" and the "Youth Self-Report (YSR)" analyzed behavioral issues.[20] The "Children's Depression Inventory" and the "Dutch versions of the Self Perception Profile" analyzed depressive symptoms and self-perception, respectively.[20] Feasibility of an EP intervention was examined[19] through a study checklist. Only one study examined the adherence to the activity program through the compilation of a log.[18] Another study examined the children's perception of the activities using an interview that includes open questions.[17]

Sleep efficiency was examined with the "Daily Sleep Diary-Parent,"[19] and another study examined the food intake through a record reviewed by phone.[22] One study examined some information about the child (such as age, gender, and thoughts about the disease) by using a "Children's Identifying Information Form" drawn up by the researchers[24] (Supplementary Table S2).

3.8 | Effects of EP on outcomes

The interventions had positive effects on cardiovascular variables,[22,24] flexibility,[18] muscle endurance/strength,[23,24] functional mobility,[18,24] motor performance,[21] and long-term effects on anthropometric factors,[21] body composition, and bone mineral density.[21] Other significant effects described were sleep efficiency[19] and the amount of physical activity and sedentary behavior.[22] The EP intervention resulted feasible during the inpatient phase for chemotherapy.[19] Modest positive effect was observed in some HRQoL parent report variables.[20] Effects on the adherence to exercise and on the children perception of the activities were not possible to understand.[17,18]

3.9 | Gaps, problems, and requirements

The main biases considered include method and design, sample, EP, outcomes, evaluation tools, and effects of EP on outcomes.

There is a lack of RCTs with protocols that followed the methodological guidelines outlined in the CONSORT statement.[28] Three studies did not blind the participants[18,19,21] and in other three studies the

randomization process was not clear or not reported.[22–24] Also, one study[18] did not clearly report difference of measures at baseline. Mistakes were present in the missing data processing.[21]

Six studies have sample bias. Three studies[17,23,24] did not report the leukemia risk type. Other biases were the limitation of the age range of patient groups,[22] the low age at the recruitment phase,[21] and the small sample size.[20,22]

Five studies had EP bias. One study[18] described a personalized individual home-based EP. Thus, children do not have the same EP and some of the Frequency, Intensity, Time, and Type (FITT) principles varied among the participants. This choice reduced the possibility to make transversal considerations on the effects of exercise on the whole patient group. Furthermore, while the authors declared that the EP was age appropriate, they did not specify how they met those criteria. Another study[19] did not use any tools such as daily activity logs to report the adherence to the home-based EP, the timing of the EP intervention was not specified, and the activities made by the control group were not clearly described. Also in this case, adherence to intervention was assessed only in every third or fifth enrolled patient.

In one study,[21] the intervention, timing, and duration of each exercise session were not specified. In another study,[23] the timing of the assessments differed between the experimental and control groups and the EP was not supervised elsewhere.[17]

Outcomes were not identified as primary or secondary outcomes. Multiple analyses of the same data created risks for false positive findings. Analyses that were prespecified in the trial protocol (primary outcomes) are much more reliable than those suggested by the data (secondary outcomes), and therefore researchers should report which analyses were prespecified.

Three studies have tools bias regarding an incomplete description of assessment instruments[18,24] and/or the utilization of a nonstandardized measurement scale.[17]

Five studies have problems concerning the effects of EP bias. In three studies,[19–21] the effects were not differentiated according to the type of cancer and in three studies the effects of EP on the outcomes were not clearly described.[21,22,24]

4 | BIAS SOLVING

The majority of the RCTs in this study had errors in the randomization process. This makes it difficult to provide correct evidence about the type of association between EP and outcomes. Randomized controlled clinical trials represent the gold standard of research in healthcare interventions, although it could be difficult to meet all the criteria proposed by the CONSORT statement.[28] Blinding the population that is receiving an EP in the same hospital might be almost impossible. However, blinding the assessors can be a good start to make assessment more objective. Sampling problems are a common bias due to the low incidence of cancer in the pediatric population, the different stages of development of children, and the different types of cancer. All these problems made the generalization of findings difficult in pediatric oncology. Future RCTs should examine the effects of EP in a large sample of childhood cancer leukemia and lymphoma subgroups to make the results more exploitable by the professional community and more tailored to specific types of patients. Multisite rather than single center studies are highly recommended.

There was considerable evidence of heterogeneity on the type and intensity of the EP among the selected studies, thus we were unable to draw conclusions regarding the best EP. However, homogeneity can be explained if we applied the principle of training. Because this review focuses on a population that was on treatment and most of the interventions were about 3 or 4 months long, the frequency, intensity, type, and time proposed in the interventions make them appropriate if we follow the progression and specificity principle. Fatigue, loss of muscle mass, and deteriorating aerobic capacity are well-known side effects of treatment. Thus, aerobic and strength training are present in most of the interventions. From a progression perspective of another important training principle, low to moderate exercise intensity should be considered appropriate as the population is on treatment and might be deconditioning with other symptoms and side effects that might limit the exercise intensity. Focus on longer studies (2–4 years) will allow researchers to show different types of programs based on the application of progression (principle of training). Another solution is to start grouping patients with common side effects, instead of cancer type, such as decreased aerobic capacity, diminished ankle dorsiflexion, decrease in strength, and osteoporosis, and come up with different types of exercise guidelines that will be specifically tailored to a pertinent side effect. Specific exercise guidelines for different types of oncological diagnoses as well as different types of stage of treatment and common side effects should always be performed worldwide as already suggested by Viña et al.[8] These guidelines will not only serve as a tool for spreading the benefits of EP during the pediatric cancer journey but also establish, common criteria to prescribe EPs for childhood cancer populations. The current state of published research suggests that there is a pressing need to provide evidence-based guidelines for those working with this population to promote exercise participation.

Finally, a combination of physical and psychosocial variables, both objective and self-reported ones, would be the best strategy.

5 | DISCUSSION

In conclusion, to date the effects of the interventions are still unconvincing, which make it impossible to draw specific suggestions about the optimal strategy to conduct EP. Although the studies presented in this review were RCTs, there is still too much variability among them in terms of study design and intervention characteristics, so further practical suggestions are mandatory.

An imaginative solution could be the design of an EP to be used as a "paradigm." An EP paradigm would allow professionals to follow precise standards of activities and procedures both regarding the methodology (i.e., randomization and participants) and the scheme and the content of the EP. An EP paradigm should exist at least for the three major categories of pediatric tumors such as hematological, solid, and brain malignancies. This paradigm can also be constructed around common types of side effects such as fatigue, decreased aerobic capacity, peripheral neuropathy, and osteoporosis. Also the paradigm should

also respond to the objectives of exercise training during different stages of treatments and thus will help to create a sense of variability and progression along different stages of treatments.

To achieve this arduous task, consideration should be given to the approach of the International Study Group,[29] a collaboration of professionals from several countries to bring international agreement on how to develop EP paradigm. It allows sharing of the same EP in several centers, thus seeking to reach a multicenter consensus. Also, the possibility to share epidemiological data on culturally diverse populations is undoubtedly another added value of this proposal. Despite its ambitious nature and the awareness about pediatric recruitment issues, the considerations on this proposal are encouraging. The study of Soares-Miranda and colleagues[30] in fact confirms the possibility to invest in a specific and standardized program for a single tumor class, which meets the quality criteria for RCTs (e.g., randomization, concurrent comparison group, blinded measurement). In fact, the proposed EP paradigm for solid tumors is also able to reach the methodological fulfillments necessary to support strong medical evidence. Specifically, this study explored the beneficial effects of EP on the immune system; it is very important because it allows new relevant insight on the positive effects of EP on immune defense, which can play an important role in tumor growth suppression. So, an EP paradigm that respects RCTs criteria is a practicable route in the pediatric oncology field.

Multicenter studies, in terms of both medical rehabilitation programs and medicine sports program interventions, are needed to highlight the unique and key role of physical exercise in pediatric oncology care as preventive and supportive care for children and adolescent patients receiving therapy and during the stages of their cancer. Finally, EPs presented in this review did not present any important detrimental effect on the health of participants. It is an important finding considering the American College of Sport Medicine call to avoid inactivity in all forms of cancer, even in those with difficult treatment or prognosis. Thus, doing regular exercise should be recommended instead of bed rest or not performing any physical activity. At the same time, the World Health Organization declares physical activity as a public health priority. As researchers, we should focus on providing guidelines that help practitioners to recommend exercise based on the evidence that we have, and advancing this would be easy as soon as exercise start to become more common in standard care.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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