Psycho-Oncology
Psycho-Oncology **18**: 440–448 (2009)
Published online 25 February 2009 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pon.1484

Development, feasibility and efficacy of a community-based exercise training program in pediatric cancer survivors

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Received: 18 April 2008
Revised: 14 August 2008
Accepted: 26 September 2008

Abstract

***Objective*: The aim of this study was to develop a 12-week exercise training program (comprising aerobic and strength exercises), and to study the feasibility and efficacy of this exercise program in children who survived acute lymphoblastic leukemia.**

***Sample and methods*: A 12-week exercise program was developed and tested for feasibility in nine children who survived cancer.**

***Results*: From the 16 eligible children for the intervention, 9 participated, while 4 were able to complete the entire program. Feasibility of the program was scored by five children, two of them reported the program as being too demanding. The participating physiotherapists were satisfied with training methodology and training progress. The efficacy of the program on muscle strength, exercise capacity, functional mobility and fatigue showed no significant differences between pre and post training.**

***Conclusion*: In designing a community-based exercise training program, not only the stage of the disease needs to be considered, but more so the age of the children, the variety of exercises, the location of implementation and even more importantly the views and motivation of the parents concerning the execution of an exercise training program. A careful balance between these parameters could lead to a greater adherence and by that, to a better outcome of these programs.**

Keywords: fitness; exercise; cancer; children; oncology

Introduction

Leukemia is a malignant disease of bone marrow in which early abnormal lymphoid cell pre-cursors (lymphoblasts) replace normal marrow hematopoietic cells. Acute lymphoblastic leukemia (ALL) is the most common form of all childhood malignancies; it comprises approximately 30% of all childhood malignancies in the United States. In Europe, the 5-year survival of ALL has increased from 71% in children diagnosed between 1983 and 1985 to 83% in children diagnosed between 1992 and 1994 [1]. In the United States survival rates of the same magnitude have been reported [2,3]. The tremendous increase in survivors of ALL during the last decades, due to the usage of more intensive systemic therapy has focused more interest on the side-effects of therapy and possible development of long-term effects. Several studies showed that survivors of ALL have reduced muscle strength and functional capacity during, as well as after treatment [4–8]. Furthermore, it was found that children who survived ALL have impaired pulmonary function and suffer from cardiac dysfunction as a consequence of cardiotoxicity of chemotherapy [9,10]. A review of van Brussel *et al.* showed that physical fitness of ALL survivors tends to be decreased [11]. Moreover, it was found that aerobic and anaerobic physical fitness, and strength of knee extensors were considerably lower in long-term survivors of ALL (5–6 years after last therapy) compared with healthy children [12].

The principal causes of reduced physical fitness and muscle strength in ALL survivors are likely to be neuropathy and myopathy; both are short-term effects of the chemotherapeutic treatment [13]. The sedentary lifestyle is considered to be another contributing factor. It was found during treatment as well as after treatment that children who survived ALL have a lower daily energy expenditure compared with healthy subjects [14–16]. The principal causes of reduced physical fitness and muscle strength in ALL survivors not only implicate consequences for daily life activities of survivors, but also for their health in adulthood. Children treated for cancer often have a reduced body height and bone mineral density, and are more obese than their healthy peers [17–19]. Particularly children who are treated with radiotherapy are more at risk for obesity, which also contributes to health risks in adulthood. Based on positive reports on rehabilitation programs in adult cancer survivors during and after chemo/radiotherapy, physical exercise has been suggested to further improve the health outcome for patients who survived cancer [20,21]. However, there is little knowledge on the role of physical exercise in the rehabilitation of pediatric oncology patients. In literature, there are only a few reports that describe the effects of an exercise program on the physical fitness of children who survived ALL or other forms of cancer. Shore and Shepard [22] studied the effects of a 12-week aerobic training program in three children who were still under treatment for various forms of cancer. They found an improvement in physical fitness, a decrease in the amount of body fat, and in the quality of life [22]. Marchese *et al.* [23] performed a study in children receiving maintenance chemotherapy for ALL. They evaluated the effects of a 4-month intervention program combining physical therapy sessions and home-based exercises (aerobic training, stretching exercises) in children with ALL. Ankle dorsiflexion range of motion and knee extension strength, both of which are important functions for normal gait, significantly improved after the aforementioned intervention. San Juan *et al.* [24,25] performed a 16-week training intervention in seven children in the maintenance phase of treatment against ALL. They found that patients with ALL in the maintenance phase of treatment can safely perform both aerobic and resistance training. Training resulted in significant increases in measures of aerobic fitness, strength, and functional mobility. Exercise capacity was partially maintained during detraining [25]. They also investigated the effects of an 8-week intra-hospital training program for children who underwent a bone marrow transplant [26]. Significant effects were found for muscle function and VO_{2peak}, as well as for muscle strength and quality of life on the self-reported domain of comfort while resilience improved [26]. Collett *et al.* [27] performed a randomized controlled trial in overweight/inactive adolescents who survived cancer. After 12 weeks of training (individualized program), there was little change in body mass index (BMI), while physical activity and fatigue slightly increased. Study participation among survivors was limited due to the commuting time and lack of commitment to center-based sessions. All studies conducted so far in children were performed in an in-patient hospital setting. We preferred a community-based exercise program because it is less time consuming for parents and patients, and might also be less expensive compared with in-patient hospital training.

The aim of this study therefore was to develop a 12-week home-based exercise training program (comprising aerobic and strength exercises) for children who survived ALL, and to study it's feasibility and efficacy.

Methods

Development of training program

Based on previous research in children and adolescents with chronic conditions [28,29] and cancer [30,31], we chose a 12-week training program. Patients were instructed to attend the 45-min exercise sessions twice a week at a local physiotherapy practice, as well as to perform home-based exercises twice a week.

The exercise sessions were supervised by local pediatric physiotherapists, who were provided an extensive manual in order to warrant the uniformity of the training program.

The program comprised three phases (Figure 1). In the first phase the main goal was to increase muscle strength, in the second phase to increase aerobic fitness, and in the third phase the focus was on interval training. Each phase lasted 4 weeks.

The training sessions started with a warm-up followed by exercises, and ended with a cool-down. The duration of the exercises and intensity of the program increased gradually throughout the program, while the duration of the warm-up and cool-down decreased. The exercise intensity was based on the guidelines of the American College of Sports Medicine [32], adapted for the oxygen uptake–heart rate (HR) relationship in children [33]. The *Moderate* and *Hard* exercise intensity domains (40–59% of $VO_{2reserve}$ and 60–84% of $VO_{2reserve}$, respectively) compares to 66–77 and 77–90% of HR_{max} in children [7].

The intensity of the training was monitored during the training sessions using a portable HR monitor (Polar Accurex Plus, Polar Oy, Kempele, Finland).

The field tests comprised the modified shuttle walk test [34], a steep ramp test on a cycle ergometer [35], the 10×5 m sprint test [36], and a 30 s repetition maximum was determined for sit-ups, push-ups, head and leg raises, and a 60 s repetition maximum for squads. The field tests were performed in local physiotherapy practices, if needed adapted to the locally available equipment and setting.

The children were instructed to exercise at home for at least two times per week. The exercises were outlined by text and photos, and verbally by one of the researchers. The home training program was

DOI: 10.1002/pon

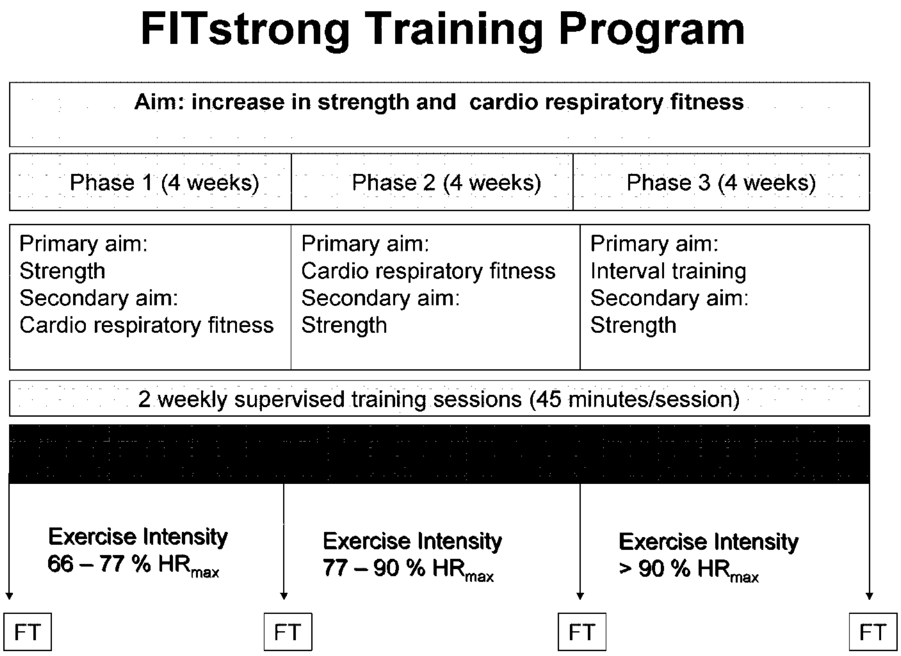

Figure 1. Outline of the FITstrong training program. HR_{max}, maximal heart rate; FT, field tests

based on the '*Royal Canadian Air Force Exercise Plans for Physical Fitness*' and was composed of five basic exercises to enhance strength, flexibility and aerobic fitness [37]. At each home training session the children accomplished five exercises a given number of times in 11 min, stepwise increasing intensity and the number of times during the 12 weeks. In a training diary the children recorded training frequency and training progression.

Table 1. Subject characteristics of included patients ($N = 9$)

	Mean	SD	Range
Age (years)	9.3	3.2	6–14
Weight (kg)	39.90	16.53	21.2–70.3
Height (m)	1.41	0.17	1.18–1.62
BMI (kg/m^2)	18.8	4.7	14.5–30.0
Σ7SF (mm)	94.65	46.50	39.8–161.2

BMI, body mass index, Σ7SF, sum of seven skinfolds.

Patients

All children aged between 6 and 18 years who were treated for ALL at the Pediatric Hematology-Oncology clinic of the Wilhelmina Children's hospital, University Medical Centre Utrecht were eligible to participate in this study. The children had to be in continued remission from ALL, and the time elapsed since their last chemotherapeutic treatment had to be at least 6 months. Children were excluded when they were still receiving chemotherapy at time of the study or when they suffered from a severe cardiomyopathy (ejection fraction <40%, ischemia and angina pectoris at rest). A sample of 16 children met all these conditions and was invited to participate in the study. Seven children and their parents preferred not to participate. Nine children were included in the study; they were aged between 6 and 14 years, their characteristics are shown in Table 1. At the time of inclusion, 12–36 months had passed since cessation of the patients' last chemotherapy. Informed consent was obtained from the parents and also from the children if they were older than 12 years of age. This study was approved by the Medical Ethics Review Committee of the UMC Utrecht (Trail Registration ♯: ISRCTN08454156).

All children were treated according to the Dutch Childhood Leukemia Study Group (DCLSG) protocol ALL-9. The children received 34 × 2.5 mg/dose vincristine during the whole treatment period of 2 years. Furthermore, they received, among other things, dexamethasone and anthracyclines as corticosteroid therapy. The protocol did not include cranial irradiation.

Patients were assessed before (T_0) and after (T_1) 12 weeks of training.

Feasibility

The feasibility of the program was measured using a questionnaire for patients/parents and for the trainers. Patients/parents answered eight questions regarding training, motivation, and enjoyment. Moreover four 10-cm visual analogue scales (VAS) were included to measure motivation, interest, pre-training fitness and post-training fitness. Trainers had to answer 24 open questions on three domains (general, instruction materials, and the exercise training program).

DOI: 10.1002/pon

Anthropometry

Body mass (kg) and height (m) of the children were measured using an electronic scale and a wall-mounted stadiometer, respectively. BMI (kg/m^2) was calculated as body mass/height^2. Skin folds (mm) were measured to determine subcutaneous adiposity. Harpenden skin fold calipers (Holtain, Crymych, UK) was used to measure skin folds at seven sites at the right side of the body (triceps, biceps, subscapular, suprailiac, mid-abdominal, medial calf and thigh), in accordance with the American College of Sports Medicine guidelines [38]. Since there are no validated prediction formulae for leukemia patients for calculating percentage of body fat [17], the sum of the seven skin folds was used as an index for body fat after Pollack *et al.* [39].

Muscle strength

Muscle strength (N) was determined using a hand-held dynamometer (Citec dynamometer CT 3001, C.I.T. Technics, Groningen, the Netherlands). Six muscle groups were measured at the right as well as at the left side of the body: shoulder abductors, knee extensors, foot dorsal flexors, hip flexors and grip strength. Maximum muscle strength was tested using the 'break' method, in which the examiner gradually overcomes the muscle strength of the patient and stops at the moment the extremity gives way. Grip strength was measured using the 'make' method. With the subjects sitting and the arms held 90° flexion at their sides, the dynamometer was gripped as strong as possible for 3 s without pressing the instrument against the body and without touching the elbow to the body. Every muscle group was measured three times at each test session; the highest score was used for analysis.

Functional mobility

The children's ability to stand up from a seated position in a chair and walk 3 m was tested using the Timed Up and Go test (TUG) [7]. In this test the children were instructed to get up from a chair and walk 3 m as fast as possible. The Timed Up and Down stairs test (TUDS) was used to assess the children's ability to navigate stairs [40]. The children had to walk up and down one flight of stairs (11 steps) as quick as possible. For safety, the children were allowed to hold onto the hand rail. The children performed both tests three times, all performance times were measured, and the mean time was used for analysis.

Cardio-pulmonary exercise test

All children performed a cardio-pulmonary exercise test (CPET) on an electronically braked cycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands) following the Godfrey protocol [41]. This protocol was selected to elicit a maximal exercise response within 6–12 min [42]. Seat height was adjusted to the patient's leg length. The test started with 1 min of unloaded cycling. After this minute, workload was increased by 10, 15 or 20 W every minute depending on the patient's height. The patients were instructed to cycle at a speed of 60–80 rpm, and encouraged to continue cycling until exhaustion. The highest achieved workload (W_{peak}) was recorded. During the test, patients breathed through a facemask (Hans Rudolph Inc, USA) connected to a calibrated metabolic cart (Cortex Metamax, Cortex-Medical, Leipzig, Germany). Expired gas passed through a flow meter (Triple V volume transducer), oxygen (O_2) analyzer, and a carbon dioxide (CO_2) analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation (vE), oxygen uptake (VO_2), carbon dioxide output (VCO_2) and the respiratory exchange ratio ($RER = VCO_2/VO_2$) from conventional equations. HR was measured continuously during the exercise test using a portable HR monitor (Polar electronics, Kempele, Finland). Maximal effort occurred when one of the two criteria were met: $HR > 180$ beats per minute or $RER > 1.0$. Peak oxygen consumption (VO_{2peak}) was taken as the average value over the last 30 s before subjective exhaustion. Relative VO_{2peak} ($VO_{2peak/kg}$) was calculated as absolute VO_{2peak} divided by body mass.

Fatigue

The CIS-20 was used to determine fatigue. It consists of 20 questions and is reliable and validated [43]. In this questionnaire the patient is asked about fatigue in the 2 weeks preceding the assessment. It is designed to measure four aspects of fatigue; subjective experience of fatigue, concentration, motivation, and physical activity. The items are scored on 7-point Likert scales (with 1 indicating best and 7 worst function).

Statistical analysis

Baseline and post-training differences were analyzed using descriptive statistics, qualitative analysis, and the Wilcoxon signed-ranks test where appropriate. Patient characteristics and feasibility were analyzed using descriptive statistics. The statistical software package SPSS 16.0 (SPSS Inc, Chicago, IL, USA) was used.

Results

Patient flow

Of the 16 eligible patients, 7 patients did not participate in the study because of time constraints

DOI: 10.1002/pon

(extra travel to hospital and/or physiotherapy practice ($n = 4$)), no interest in physical activity (1), or they wanted to leave the disease behind ($n = 1$). One family could not be contacted because of a relocation.

Nine children were included in the study; all children were able to complete the baseline tests. Their characteristics are provided in Table 1. After the baseline test, one patient dropped out because of a problematic social family context (divorce). Eight children (three boys, five girls) started training under supervision of a local physical therapist. During the training period, four girls dropped out after 1, 4, 6, and 6 training sessions, respectively (Figure 1).

The primary reason of the girls to stop training was that they found the two sessions per week physically too demanding and/or difficult to combine with school attendance and their other activities. One girl stopped training after one session because her mother did not support the program (Figure 2).

Feasibility

The feasibility of the training program for the children can be appreciated from Table 2. Only children/parents who finished the training program returned the questionnaires. Four children reported a variety of physical symptoms during the training (headache, muscle soreness, fatigue, and hyperventilation). All seven physiotherapists who were actually involved in the training program returned the questionnaire (Table 2). Seventy percent of the trainers were satisfied with the training methodology, variety of training activities, and compliance of the children who finished the program. Concerns were expressed about the level of fatigue expressed by the children, training duration, necessary training equipment, and lack of variation of home training program by the majority of the trainers (70%). There was a unanimous agreement on the training progress made by the children.

Efficacy

The efficacy of the exercise training on muscle strength, exercise capacity, functional mobility, and fatigue are provided in Table 3. No significant differences were found between pre and post training.

Discussion

The objective of this study was to develop a 12-week community-based exercise training program (comprising aerobic and strength exercises) for children who survived ALL and to study it's feasibility and efficacy.

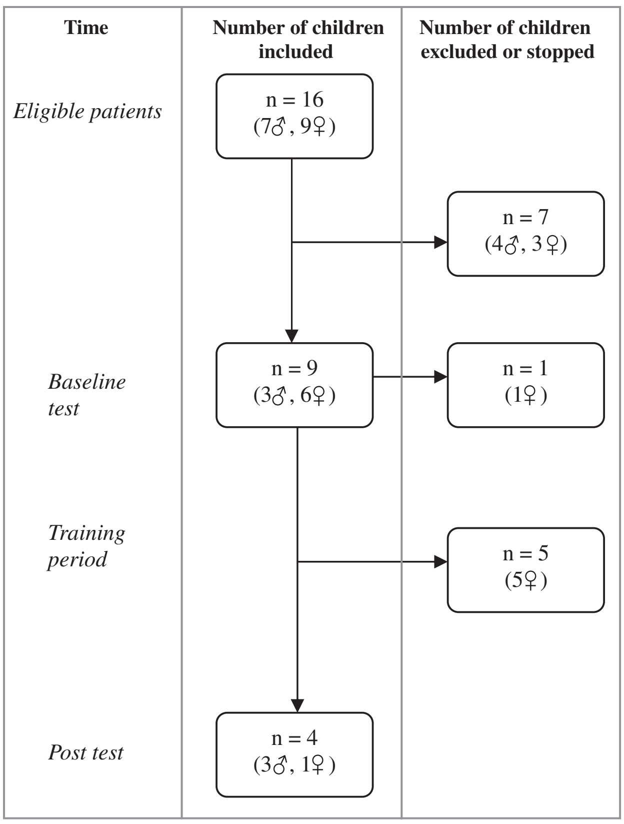

Figure 2. Flow chart visualizing subject flow in this study

DOI: 10.1002/pon

The majority of the physiotherapists had to change the prescribed training sessions for various reasons at one or more points during the program. The younger children sometimes perceived the training program as boring, resulting in a decreased motivation. To overcome this, more variation and exercises by means of games were introduced in the program. Another reason for adapting the program was the non-availability of equipment (i.e. a cycle ergometer, bench) at the local physiotherapy practices required to implement the exercises as described in the instruction manual. As a consequence of these changes, the gradual increase of intensity of the exercises to elicit a training effect might have been interrupted or even have caused a permanent decrease in training intensity. Most children found the home training program boring, and could not be motivated to complete the entire program. It might, in part, explain why physical fitness and muscle strength was not improved after training. In the current study, four girls dropped out. The three elder girls (respectively 11, 12, and 14 years old) stopped because they found the training sessions too intensive and hard to combine with their other activities. This might indicate that the frequency of training (two times per week) is too much for children who are also participating in other social activities. However, two training sessions per week is the absolute minimum to elicit a training effect in children [29]. To prevent training sessions becoming too intensive, a more gradual increase of intensity is advised. We have to bear in mind however that training means pushing physiological borders and logically as a result of that the child will be fatigued. Therefore, it is important that parents support the program of their children and that they are very motivated. In parents of survivors of ALL, this usually is a problem, as parents were found to be very concerned and protective about health and well-being of their children [44,45]. In a qualitative study of Van Dongen-Melsman *et al.*, the impact of childhood cancer on parents after cessation of treatment, and the way they cope was assessed [45]. Most parents in this study regarded their child as very vulnerable. At a physical level, this resulted in restricting childhood daily activities to prevent possible harm. At psychological level, this led to setting less demands on their child, trying to compensate for the many unpleasant events during treatment and to protect their child from more unhappy or stressful events [45]. This protective behavior of parents continued for many years after the end of treatment. The fourth, younger girl stopped training because her mother did not find it necessary for her to participate in the training sessions, even though her father did find it useful. The high number of drop-outs found in our and in other studies [27,46] is indicating that it is sometimes hard to keep children and their parents motivated to complete a community-based training program,

Table 2. Feasibility of the program scored by patients and physical therapists

Patients	
Mean training duration (max 24 h)	14.8 h (60% of max)
Perceived training effort (range 0–10)	8.1 (range 4.8–10)
Perceived effort center-based training	Fun but demanding ($n = 3$) Boring and demanding ($n = 1$)
Perceived effort Home Exercise Program	Fun but demanding ($n = 1$) Boring and demanding ($n = 4$)
Physical therapists	
Mean participation duration	14.3 (range 0–24) h
Quality of the program (0–10)	7.0 (range 7.0–8.0)
Clarity of the instruction (0–10)	7.7 range (7.0–9.0)

Table 3. Efficacy of the exercise training

Outcome	Pre training Mean ± SD	Post training Mean ± SD	% change from baseline Mean (range)
BMI	18.1 ± 2.7	18.4 ± 2.7	2 (0–4)
Muscle strength			
Shoulder abductors (N)	88.0 ± 21.2	97.5 ± 26.8	10 (−2 to 18)
Knee extensors (N)	194.6 ± 45.7	184.8 ± 52.0	−6 (−13 to 4)
Hip flexors (N)	168.8 ± 46.4	157.4 ± 37.0	−4 (−21 to 13)
Foot dorsal flexors (N)	114.4 ± 44.0	118.8 ± 51.0	3 (−8 to 12)
Grip strength (N)	69.3 ± 22.1	62.8 ± 23.4	−10 (−21 to 1)
Exercise capacity			
W_{peak} (W)	107.5 ± 57.2	105 ± 56.1	0 (−14 to 25)
VO_{2peak} (ml/kg/min)	35.5 ± 9.1	34.25 ± 5.6	3 (−7 to 25)
Functional mobility			
TUG (s)	1.55 ± 0.28	1.62 ± 0.17	4 (−5 to 23)
TUDS (s)	7.7 ± 2.7	7.7 ± 2.1	−1 (−9 to 7)
Fatigue			
CIS-score	41.5 ± 14.7	36.8 ± 21.7	−11 (−37 to 26)

BMI, body mass index (kg/m^2); W_{peak}, peak work load; VO_{2peak}, peak oxygen uptake; TUG, Timed Up and Go; TUDS, Timed Up and Down Stairs.

especially in a very protective environment. After the training period, no changes in aerobic capacity or muscle strength were found. This result is in contrast with the results of the few preceding studies concerning training of pediatric cancer patients during and after treatment [22,24,25,31]. However, in the study of San Juan *et al.*, all children were in the maintenance phase of treatment, and in the study of Shore *et al.* four out of six children still received chemotherapy during the study. Particularly in the study of San Juan all children had a lower $VO_{2peak/kg}$ at baseline (24.3 ml/kg/min) [24,25], which is significantly lower compared with the participants in our study, and which give them a larger room for improvement compared with our study population. Moreover, it is likely that a part of their improvement is due to natural recovery from the intensive chemotherapeutic treatment. A recent study of Collett *et al.* found no significant effects of a 12-week training program on BMI, health-related quality of life, physical activity, and fatigue in pediatric cancer survivors. They also experienced problems with study participation due to the commute and time commitment for center-based sessions [27]. These results and problems are in agreement with those encountered in our current study. In previous studies it was found that BMI growth rates increased, and physical fitness decreased during the summer vacation [47,48]. The measurements at T1 were performed one month after summer holidays. In our current study, training sessions were less regular or even stopped during the summer break as a result of holiday trips of some children and physical therapists. Furthermore, school gym and activities at sport clubs were also stopped during holidays, while Dutch weather did not permit outside activities. All these factors might have contributed to a decrease or a lack of increase in physical fitness parameters after the training period.

Recommendations for future research

Although the current study failed to find a positive effect of exercise on physical fitness of survivors of ALL, the reduction of $VO_{2peak/kg}$ in our and earlier studies indicates that there seems to be a need for a physical training program. However, before including a training program in the standard treatment rehabilitation protocol of ALL patients, further research is needed. In the Netherlands it is impossible to plan a 12-week training program without interrupting school holidays. A training program should therefore be planned before or immediately after summer holidays. In this way, the children can train regularly and no long periods of detraining occur. Another way to increase the efficacy is individualization of the training program. After baseline measurements, it can be evaluated which aspect of physical fitness needs to be improved, and thus what the focus of the patient-tailored physical training program should be. Furthermore, younger children are probably challenged and motivated by different exercises than older children; this should be considered in designing the training programs. Also whether a home-training component should be part of the training program, since it is very hard to motivate the children to do their regular home exercises. When children have fun when doing the exercises, compliance to the program might be better. In future research, it is important to include a psychosocial component for both parents and children. Parents and children should be extensively instructed about the benefits of physical exercise. Furthermore, they should be informed about the short-term side effects of training such as muscular pain and tiredness, and that these short-term effects do not harm the child. Moreover, the parents should be informed that excessive over-protection of their child is not necessary, and that it is safe for their child to be physically active, and to participate in school gym, sports, and other physical activities such as walking, cycling, and hiking. In addition, it should be emphasized that they, as parents, have an important role in encouraging their children to participate in these activities and provide support to proceed with the training program.

An interesting option is exercise training during the maintenance phase of treatment. This phase is less intensive than the induction and intensification phases of treatment, and due to the less intensive character, children experience less side effects and are able to participate in a training program. A number of patients in the maintenance phase of treatment are already successfully trained at our Department. Moreover, the studies of San Juan *et al.* proved that these patients can be successfully trained [24,25]. It seems justifiable to conclude that in-hospital exercise training interventions is the first option in this specific patient group.

When normal values of physical fitness of survivors of ALL are restored during or shortly after treatment, they are presumably better physically prepared for participation in school and social life again.

Conclusion

Our study revealed important clues concerning the physical training of pediatric ALL survivors. In designing such a program, not only the stage of the disease needs to be considered, but more so the age of the children, the variety of exercises, the location of implementation, and even more importantly the views and motivation of the parents concerning the execution of a physical activity program. A careful

DOI: 10.1002/pon

balance between these parameters could lead to a greater adherence and, by that, to a better net result of these programs.

Acknowledgements

This study was funded by a grant from the Scientific College Physiotherapy of the Royal Dutch Society for Physiotherapy (Wetenschappelijk College Fysiotherapie, Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF)) and the ROPARUN foundation.

We would like to thank the children, parents, and trainers for their participation in this study.

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