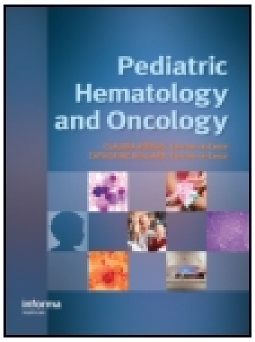

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ORIGINAL ARTICLE
Late Effects

Physical Activity and Late Effects in Childhood Acute Lymphoblastic Leukemia Long-Term Survivors

N. Bertorello, PhD, MD, R. Manicone, MD, C. Galletto, MD, E. Barisone, MD, and F. Fagioli, MD

Division of Pediatric Onco-Hematology and Cell Stem Transplantation, Regina Margherita Children's Hospital, Turin, Italy

In the present study the authors evaluated therapy-related long-term adverse effects and physical activity in a cohort of long-term survivors of childhood acute lymphoblastic leukemia (ALL), diagnosed in their center between March 1991 and August 2000, treated according to the AIEOP (Associazione Italiana di Ematologia e Oncologia Pediatrica) ALL 91 or 95 study protocol and regularly seen in the authors' long-term follow-up unit. The authors analyzed the long-term sequelae of major body systems in this cohort of subjects and administered an "ad hoc" questionnaire concerning sport. The authors found that 70 patients out of 102 (68.5%) showed no late effects, 10% presented only instrumental or neuropsychological test abnormalities, and 21.5% had 1 or more clinical late sequelae. None of the evidenced late effects represented a contraindication to do physical activity. Sixty-one percent of survivors do physical activity, most of them regularly. Sixty-one percent of males and 18.5% of females ($P < .005$) do competitive sport (sports rates are similar to those of the general age-matched population). Nearly all subjects spontaneously choose to do sport and think physical exercise is an important and useful resource for their health. The authors conclude that the more recent therapy regimens for leukemia treatment, excluding bone marrow transplantation, do not seem to cause such late effects as to prevent survivors from doing sport. Therefore, in the care of ALL survivors, physical activity is not only not contraindicated, but should also be promoted as much as possible. The development of specific educational programs is warranted as part of the care of cancer survivors.

Keywords acute lymphoblastic leukemia, childhood, late effects, long-term survivors, physical activity, sport

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy [1]. Today, over 75% of children diagnosed with ALL are cured and the number of adult survivors of childhood leukemia is steadily increasing. ALL treatments could cause long-term sequelae in childhood cancer survivors [2–19] and some of which have direct consequences on the capability to practice sports. Anticancer therapy may affect central cardiac dynamics and thus the blood supply to body tissues, particularly exercising muscles. Anthracyclines can induce myocardial damage with subsequent decreases in cardiac output [20, 21]. Methotrexate (MTX) may cause lung damage

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Address correspondence to Nicoletta Bertorello, Division of Pediatric Onco-Hematology and Cell Stem Transplantation, Regina Margherita Children's Hospital, Piazza Polonia 94, 10126, Turin, Italy. E-mail: nicolettabertorello@libero.it

[22] and cyclophosphamide can lead to pulmonary fibrosis [23]. Mediastinal radiotherapy or lung infections during, or subsequent to, leukemia treatment can reduce total lung capacity [24, 25]. Muscle atrophy may develop due to the catabolic effects of several chemotherapeutic agents such as MTX, vincristine (VCR), or corticosteroids [26–28]. VCR and corticosteroids can be also responsible for a reduction in muscle strength. After immunosuppressive therapy, impaired aerobic metabolism or reduced capillarization has also been described [29]. Furthermore, corticosteroid therapy increases adiposity and body mass in children receiving treatment for ALL, leaving a condition of obesity in survivors. Muscle atrophy and obesity are aggravated by sedentary habits. Survivors do not often do physical activity because of low self-esteem or because, when they were children, parental overprotection caused an underestimation of their own potential for performing physical tasks [30]. Therefore, the physical activity of ALL survivors might be lower compared to healthy subjects of the same age.

There is definitive evidence that sport does improve fitness and reduces cardiovascular morbidity and mortality [31]. Physical activity seems to reduce significantly the risk of developing other chronic diseases such as obesity, osteoporosis, diabetes, and depression [32]. Furthermore, sport represents a mechanism to reduce time spent in sedentary activities, aids coordination, balance, and flexibility, and improves stamina, concentration, and sleep quality. Thus, exercise can be an effective strategy to improve the quality of life in both healthy and in ill people [33–36].

The aim of this study was to evaluate the incidence and characteristics of physical activity in a cohort of long-term survivors of childhood ALL and to determine how much therapy-related long-term adverse effects influence the ability to practice sport in these subjects.

MATERIALS AND METHODS

The patients included in this single-center cross-sectional study fulfilled the following criteria: diagnosis of ALL in our center between March 1991 and August 2000; age under 18 years at the time of diagnosis; treatment in our center according to the AIEOP (Associazione Italiana di Ematologia e Oncologia Pediatrica—The Italian Pediatric Onco-Hematologic Association) ALL 91 or 95 study protocol not including treatment with bone marrow transplantation (BMT); a follow-up time of over 5 years after the end of chemotherapy; regular controls by our long-term follow-up unit; written informed consent obtained.

The AIEOP ALL 91 protocol was administered between March 1991 and April 1995, and the AIEOP ALL 95 protocol thereafter. Both protocols consist of a BFM (Berlin-Frankfurt-Münster) backbone with 4 phases: induction (protocols Ia and Ib); consolidation (protocol M); reinduction (protocol II), and continuation (maintenance) [37, 38].

Since the end of chemotherapy, patients have been monitored as follows.

Cardiological evaluation: The echocardiographic assessment (ECHO) of the heart volume and function (shortening fraction) and electrocardiogram (EKG) were carried out at the end of therapy (OT) and after 2, 5, and 10 years.

Endocrine evaluation: Height, weight, Tanner stage, testicular volume (Prader orchidometer), pubertal onset, sexual function, menstrual/pregnancy history, and semen analysis (basal assessment) and luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, free thyroxine (FT4), thyroid-stimulating hormone (TSH), somatomedines, cortisol, and glycemia dosages were evaluated at OT. The basal assessment was repeated yearly or, if necessary, more frequently. Thyroid ultrasonography was performed when indicated by the endocrinologist.

Neurological and neuropsychological evaluation: Neurological examination, brain computed tomography (CT) scan and electroencephalogram (EEG) were performed at OT and after 2 years and a magnetic resonance imaging (MRI) was performed after 5 years. A neuropsychological evaluation was made when indicated.

Respiratory tract evaluation: A chest x-ray at OT.

Bone and joint health evaluation: A skeletal x-ray at OT.

Gastroenteric tract evaluation: Abdominal ultrasonography and complete liver assessment at OT.

Urinary tract evaluation: Abdominal ultrasonography, creatinine, and electrolytes dosage at OT; yearly blood pressure measurement and urinalysis were carried out.

Ophthalmological evaluation: An ophthalmological evaluation was performed at OT and after 2 years.

Infections from blood/serum products: Hepatitis surface antigen (HbsAg), hepatitis B and C and human immunodeficiency virus (HIV) antibodies were determined at OT and after 1 year.

Secondary benign or malignant neoplasms: Acute myeloid leukemia, myelodysplasia, lymphomas, thyroid carcinomas, meningiomas, melanomas, and breast cancer might most frequently arise in subjects treated for ALL, especially in case of radiotherapy (RT) treatment. A history of suggestive symptoms, physical inspection, and instrumental evaluations were used when appropriate.

All the scheduled evaluations are summarized in Table 1.

Survivors were followed up by a pediatric oncologist once a year from the 6th to the 10th years after the end of therapy and thereafter every 2 years until the age of 18. After this time, the subjects were then seen by an adulthood endocrinologist who made a risk-based schedule of hematological and/or instrumental evaluations for each patient.

In order to collect data concerning physical activity, the survivors over 18 years or the legal guardians of younger survivors received a phone call to inform them about

TABLE 1 Follow-up Evaluations: Type and Timing From the End of Chemotherapy

	Years from the off therapy				
	0	1	2	5	10
ECHO-EKG	x		x	x	x
Brain CT	x		x		
EEG	x		x		
MRI				x	
Chest x-ray	x				
Skeletal x-ray	x				
Abdominal ultrasonography	x				
Ophthalmology evaluation	x		x		
Endocrine evaluation			Yearly*		
Neurological evaluation	x		x		
Biochemical tests**	x				
Viral serology***	x	x			
Urinalyses	Yearly				
Blood pressure measurement	Yearly				

*More frequently, if necessary.
**Serum creatinine and electrolytes, complete liver assessment.
***HbsAg, hepatitis B and C and HIV antibodies.
CT = computerized tomography; ECHO = echocardiogram; EKG = electrocardiogram; EEG = electroencephalogram; MRI = magnetic resonance imaging.

the study and the procedures employed. Subjects who agreed to take part in the study were mailed an "ad hoc" questionnaire and a consent form that was to be completed and returned using a stamped addressed envelope. The questionnaire asked whether the survivors did sport or not and the reasons for their choices, the kind of competitive or noncompetitive sport they did, the frequency and the duration of the sport, and why they thought sport could be useful to them. To enhance the response rate, a follow-up telephone call was made to nonresponders after 28 days from the first mailing. The study was approved by the local ethical committee.

Statistical Analysis

Chi-square test or Fisher exact test were used as appropriate. Two-sided tests of hypotheses were used. P values less than.05 were considered statistically significant. Leukemia-free survival, event-free survival, and overall survival from diagnosis were estimated with the Kaplan-Meier method. Relapse was considered an event in the leukemia-free survival analysis; death in induction, treatment resistance, relapse, death in ongoing complete remission and secondary malignancy in event-free survival analysis, whereas only death was considered for the overall survival. If no event was noted, the observation time was censored at the last follow-up date. The follow-up was updated to February 28, 2009. The SPSS-PC (13.0 version, SPSS) statistical software program was used for the analysis.

RESULTS

Between 1991 and 2000, 197 consecutive children (110 males [M], 87 females [F]; median age 5 years, 8 months; range 3 months to 17 years) were diagnosed with ALL and treated in our Center. Children diagnosed between 1991 and 1995 ($n = 85$; 46 M, 39 F; median age 5 years, 3 months; range 4 months to 14 years) received the AIEOP ALL 91 protocol. Children diagnosed between 1995 and 2000 ($n = 112$; 64 M, 48 F; median age 6 years, 2 months; range 10 months to 17 years) were treated with the AIEOP ALL 95 protocol.

Out of the 85 children treated with the ALL 91 protocol, 28 (33%) relapsed after the frontline protocol and 22 patients (26%) died. Overall survival (OS), event-free survival (EFS), and leukemia-free survival (LFS) at 10 years from diagnosis were 75% (SE = 47%), 66% (SE = 51%), and 67% (SE = 52%), respectively. At the time of analysis (January 2009), the median follow-up time was 13 years, 9 months.

Out of the 112 children treated with the ALL 95 protocol, 2 patients (1.7%) were resistant to the induction phase, 24 patients (21%) relapsed after the frontline protocol, and 18 (16%) died. The OS, EFS, and LFS at 10 years from diagnosis were respectively 85% (SE = 34%), 74% (SE = 42%), and 77% (SE = 41%). At the time of the analysis (January 2009), the median follow-up time was 10 years, 1 month.

The cumulative overall survival rates in the AIEOP ALL 91 and ALL 95 study protocols are given in Figure 1.

Out of the 85 children treated with the ALL 91 Protocol, 28 patients relapsed, 6 received bone marrow transplant (BMT) in first complete remission (CR) and 9 patients were lost to follow-up: 42 patients in this group were evaluated as long-term survivors. Out of the 112 children treated with the ALL 95 protocol, 2 patients were resistant to induction, 24 relapsed, 7 patients received BMT in first CR, and 19 were lost at follow-up; 60 patients of this group were evaluated as long-term survivors. One hundred and two patients have been followed-up in our long-term survivor Outpatients Unit (53 M, 49 F; median age 17 years, 7 months; range 10 to 30 years), with a mean follow-up time of 13 years, 1 month. In this cohort of subjects, 70 patients (68.5%) had no late effects,

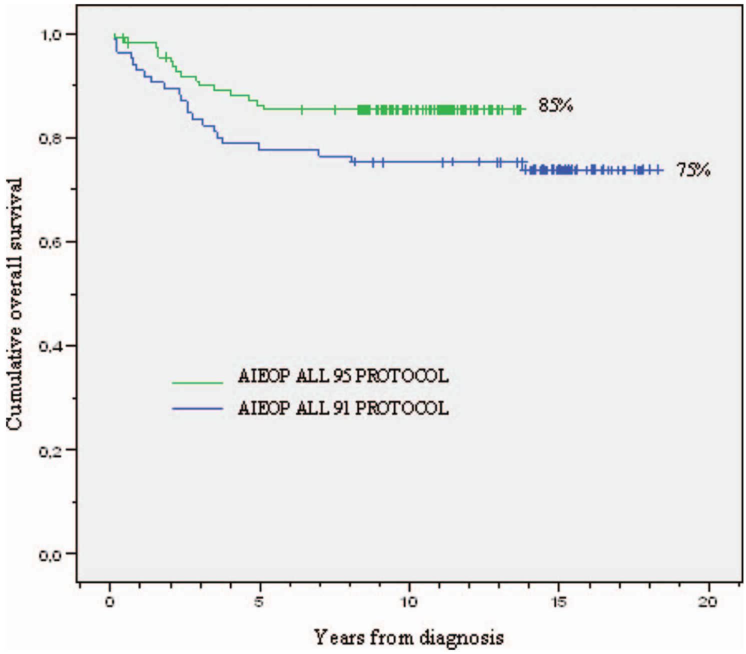

FIGURE 1 Overall survival (OS) of children enrolled in the AIEOP ALL 91 and ALL 95 study protocols.

10 (10%) showed only instrumental (8 patients) or neuropsychological test (2 patients) abnormalities and 22 (21.5%) presented 1 or more clinical late sequelae.

Five percent of the survivors showed a slight abnormality at the ECK or ECHO evaluation. Endocrine impairments were present in 9 cases (9%). Three subjects (3%) presented central nervous system impairments (2 cases of absence seizures and 1 cavernous hemangioma). The neuropsychological impairments found were deficit of short- and long-term memory with a reduction of the intelligence quotient (IQ) (2 patients), neurocognitive impairment only evidenced by a neuropsychological evaluation (2 cases), and cyclothymia, tic disorders, and dyslexia (1 case each). Bone and joint disorders were diagnosed in 3 subjects (3%). Cataract was found in a Down syndrome patient. The only case of chronic hepatitis B was probably not related to the transfusions made during the treatment, as was found in a patient with a normal hepatitis B virus (HBV) pattern at OT and after 1 year. Three subjects (3%) (mean age at diagnosis 16 years, 4 months) developed secondary neoplasms: One malignant melanoma occurred in a female 7 years after OT and was treated with surgery. One femoral Ewing sarcoma diagnosed 13 years after OT and treated with surgery and chemotherapy. One thyroid papillary carcinoma diagnosed in a male 8 years after OT and treated with surgery and 131I radiometabolic therapy. All the patients were alive in complete remission at the time of the study.

No impairments of the gastroenteric, urinary, or respiratory tracts were found.

All the developed late effects are resumed in Table 2.

Out of the subjects who answered the questionnaire about sport (48 M, 47 F; median age 18 years, 1 month; range 10 to 30 years), 58 (61%) do physical activity (31 M, 27 F; $P > .05$; median age 18 years, 1 month; range 10 to 30 years). Fifty-six subjects (98%) decided to do sport themselves and 2 (2%) took up sport on their doctors' advice. Nineteen out of 58 subjects (33%) have being doing sport for less than 3 years, 29 (50%) for 3 to 6 years, and 10 (17%) for more than 6 years. Thirteen subjects (22%) do

TABLE 2 Late Effects Following ALL Treatment in 102 Patients

	Patients	Sex		Treatment	
	n	M	F	Only CT n	CT + CRT n
ECHO/EKG abnormalities	5	4	1	5	0
Short stature	1	1	0	0	1
Overweight	3	2	1	2	1
Central hypothyroidism	1	0	1	1	0
Puberty precocious	3	1	2	2	1
Hypermenorrhea	1	0	1	1	0
Central nervous impairments	3	2	1	1	2
Neuropsycological impairments	7	4	3	4	3
Osteopenia	2	1	1	2	0
Osteonecrosis	1	0	1	1	0
Cataract	1	0	1	1	0
Chronic hepatitis B	1	0	1	1	0
Secondary neoplasms	3	1	2	3	0
Total number	32	16	16	24	8

sport more than 3 times a week, 39 (67%) from 1 to 3 times a week and 6 (11%) only occasionally. Five survivors (5%) only did sport in the past. Thirty-six subjects (62%) do 1 physical activity and 22 (38%) more than 1 (no differences between males and female were found). Among the males, the most frequent physical activities are soccer (42%) and swimming (19%), whereas dancing (33%) and swimming (30%) are the most common sports among females. Nineteen out of 31 males (61%) and 5 out of 27 females (18.5%) do competitive sport ($P < .005$). Soccer (50%) and dancing (80%) are the most common competitive sports in males and females, respectively. Thirty-seven subjects out of 95 (39%) do no physical activity at all (17 M, 20 F; median age 18 years, 10 month; range 11 to 27 years). Sixteen (44%) do not practice sport because of lack of time, 10 (27%) because they do not like it, 7 subjects (19%) because of laziness, 2 (5%) because of slight physical problems, and 2 (5%) because they do not feel up to physical effort. Out of 22 subjects with at least 1 impairment, 19 (86%) answered the questionnaire and 13 of them (68%) do not practice any sport: 7 (54%) because of lack of time, 5 (38%) because of laziness, and 1 subject (8%) because of slight clinical problems unrelated to the past cancer disease. A significant difference ($P = .004$) was found between the number of subjects with ($n = 6$) and without ($n = 52$) impairments who do sport among the 95 long-term survivors who answered the questionnaire. Although a trend ($P = .07$) was found of the influence of the cranial radiotherapy (CRT) in performing ($n = 1$) physical activity or not ($n = 4$), it was not statistically significant. No differences were evidenced between the patients treated with high-risk protocols (higher doses of corticosteroids, a major component of ALL therapy) and the others.

To the questions as to whether why the survivors think sport might be useful to them, only 1 subject (1%) answered that physical activity is useless. Of the other 94, 65 (68%) answered that sport is useful because it is enjoyable, improves health, and helps them to socialize. Nineteen subjects (20%) think it is important mainly because it improves health and 10 (11%) said it is only important because it is enjoyable.

Table 3 summarizes the main features of 58 subjects practicing sport.

DISCUSSION

Practicing sport contributes to a child's health, level of fitness, self-esteem, and success in, and the enjoyment of, recreational, educational, and social pursuits. Exercise has

TABLE 3 Physical Activity: Main Features of 58 Subjects Cured for ALL

Features		Number of patients	%
Sex	Males	31	53
	Females	27	47
Years of attendance	<3	19	33
	≥3	39	67
Times a week	≤3	45	78
	>3	13	22
Practised sports	1	36	62
	>1	22	38
Kind of sport	Competitive	24	41
	Noncompetitive	34	59
Presence of impairments	Yes	6	10
	No	52	90

been shown to improve cardiovascular fitness, muscle strength, body composition, fatigue, anxiety, depression, happiness, and several other components of quality of life also in cancer survivors [39]. Physical inactivity may, however, increase the risk of specific conditions predisposed by cancer treatment [40].

The possibility of facing late effects makes long-term survivors an "at-risk" population for reduced physical activity and it can have a significant impact on their overall quality of life and on society at large. The importance of enhancing physical activity during cancer treatment is well known [41–43]. However, to our knowledge, the great importance of physical exercise has yet to be shown in the long-term survivor population and still remains to be considered as an essential part of quality of life. Other authors who treated this argument have focused their attention on the physical skills of the subjects cured for childhood leukemia [44–47]. To date, no information concerning the main characteristics of physical activity has been provided in ALL long-term survivors and this study is the first specific and complete questionnaire to be drawn up and administered to these subjects.

Here, we have provided evidence that in our long-term childhood leukemia survivors, sport rates were similar to those of the general age-matched population (the latest national data reported that 60% of young people (aged between 6 to 15) do physical activity and that 40% do not practice any sport) [48]. Fifty percent of the subjects have been doing sport for a rather long period (3 to 6 years) and most of them practice sport regularly (1 to 3 times a week). Nearly all the subjects spontaneously choose to do sport and think that physical exercise is useful and that it is an important resource for their health. The percentage of cured people practicing sport who do more than 1 physical activity (38%) is similar to that of the general population (33%) and nearly a half of the subjects, especially males, do competitive sport.

In the group of 37 survivors who do not practice any sport, the most common reasons for not doing physical activity are a lack of time, laziness, or simply the fact that the subjects do not like sport. Only 21.5% of our survivors presented 1 or more late sequelae due to chemotherapy. None of these late effects represented a contraindication to do sport. A significant difference was found between the number of subjects with and without sequelae who do sport. Although 68% of the subjects with at least 1 impairment do not do sport, none of them do not practice sport because of clinical problems related to their past cancer experience. Neurological damage may contribute to motor impairment and disability, but we did not note any significant correlation between not doing sport and cranial irradiation. This might be due to the low number of the subjects who received CRT even though other studies also failed to demonstrate a significant correlation between CRT and gross motor performance [28] or motor skills [48].

In conclusion, the more recent therapy regimens for leukemia treatment, excluding bone marrow transplantation, do not seem to cause such late effects as to prevent survivors doing sport and a growing body of literature supports the notion that regular physical activity is safe and has potential benefits for both adult and pediatric hematological cancer survivors [49]. Therefore, in the care of childhood ALL survivors, exercise training is not only not contraindicated, but should be promoted as much as possible. During the meeting dedicated to those patients who are at the end of cancer treatment, the cured subjects should be encouraged to adopt a physically active lifestyle and the oncologist should clearly inform either the patients and/or their parents about the positive impact of such a lifestyle on their health. A review paper clearly highlighted the lack of exercise guidelines for cancer survivors [50]. These subjects should exercise less intensely and increase their workout at a slower rate than people who did not get cancer treatment. The goal is to keep up as much activity as possible, but to do it safely and to make it work for everyone (www.cancer.org). It therefore would be important to involve dedicated exercise scientists and physiologists in developing systematic and specific training programs so that the achievement and maintenance of adequate fitness levels become part of cancer survivor care.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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