Research article/Raziskovalni prispevek

FINAL HEIGHT AND BODY MASS INDEX AFTER TREATMENT FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

KONČNA VIŠINA IN INDEKS TELESNE MASE PRI BOLNIKIH, ZDRAVLJENIH ZARADI AKUTNE LIMFOBLASTNE LEVKEMIJE V OTROŠTVU

Nina Bratanič[1], Nataša Uršič-Bratina[1], Mojca Žerjav-Tanšek[1], Janez Jazbec[2], Lorna Zaletel-Zadravec[3], Ciril Kržišnik[1], Tadej Battelino[1]

[1] Clinical Department of Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, Vrazov trg 1, 1525 Ljubljana

[2] Department of Oncology and Hematology, University Children's Hospital, Vrazov trg 1, 1525 Ljubljana

[3] Institute of Oncology, Zaloška 2, 1525 Ljubljana

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Key words *acute lymphoblastic leukemia; height; body mass index; pubertal development*

Abstract

Background *Newer and more agressive forms of chemotherapy and newer protocols in the treatment have increased the survival rate of children with malignancies. Improved survival rates in children treated for acute lymphoblastic leukemia have focused attention on late effects including disorders of growth and puberty, and development of overweight or obesity.*

Methods *The height and weight expressed as body mass index (BMI) of 47 patients (29 girls, 18 boys) long-term survivors of childhood lymphoblastic leukemia was retrospectively analyzed. Height standard deviation score (HSDS) according to Tanner and body mass index standard deviation scores (BMISDS) before treatment and at follow-up were calculated. At the time of analysis all patients remained in first remission. Twenty-eight patients had cranial radiation with 12–18 Gy and 15 with 20–30 Gy. Four patients had no radiotherapy. All patients were treated with standard chemotherapy including intrathecal Methotrexat. Mean age (SD) at the diagnosis was 5 5/12 (3 2/12) years, range (5/12 – 12 5/12) and at the time of evaluation 17 11/12 (3 9/12) years, range (10 1/12 – 31 6/12).*

Results *We observed significant decrease in HSDS from diagnosis to the final height in both radiation groups ($p < 0.01$) but the decrement in final height was similar with both radiation dose regimens. The decrement in final height SDS was greater in patients treated at a younger age (Pearson, $p < 0.01$). Girls treated with higher radiation dose (20–30 Gy) were more severely affected than boys. In both radiation dose treatment groups there was a significant increase in BMISDS between diagnosis and final height ($p < 0.0001$) with no significant difference between treatment groups. Menarche occurred earlier in girls than normal with no significant difference between both radiation dose regimens.*

Conclusions *We observed significant deterioration in HSDS and increment in BMISDS regardless to the radiation dose.*

Corresponding author / Avtor za dopisovanje:

Prof. Tadej Battelino, MD, PhD, Clinical Department of Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, 1525 Ljubljana, Vrazov trg 1, Slovenia

Ključne besede *akutna limfoblastna levkemija; višina; indeks telesne mase; pubertetni razvoj*

Izvleček

Izhodišča *Z razvojem novih kemoterapevtikov in shem zdravljenja se preživetje in življenjska doba bolnikov z rakom povečujeta. S spremljanjem bolnikov se veča znanje o možnih poznih stranskih učinkih zdravljenja. Pri otrocih in mladostnikih, zdravljenih zaradi akutne limfoblastne levkemije, lahko kemoterapija in obsevanje vplivata tudi na rast in pubertetni razvoj ter nastanek čezmerne prehranjenosti ali debelosti.*

Metode *Retrospektivno smo analizirali končno telesno višino in maso, izraženo kot indeks telesne mase (ITM), pri 47 bolnikih (29 deklicah), ki so se zdravili na Onkološkem oddelku Pediatrične klinike zaradi akutne limfoblastne levkemije v otroštvu. Telesno višino in ITM smo izrazili kot standardni odklon od povprečja za starost in spol in primerjali vrednosti pred začetkom zdravljenja in ob končni telesni višini. V času raziskave so bili vsi preiskovanci v prvi remisiji bolezni. Osemindvajset bolnikov je prejelo profilaktično obsevanje osrednjega živčevja v skupnem odmerku 12–18 Gy in 15 v skupnem odmerku 20–30 Gy. Štirje preiskovanci niso prejeli profilaktičnega obsevanja. Vsi preiskovanci so prejeli kemoterapijo po standardnih protokolih ter intratekalnimi aplikacijami metotreksata. Ob diagnozi je bila povprečna starost (standardni odklon) preiskovancev 5 5/12 (3 2/12) let, razpon od (5/12 – 12 5/12), v času raziskave pa 17 11/12 (3 9/12) let, razpon od (10 1/12 – 31 6/12).*

Rezultati *Pri obeh skupinah obsevanih bolnikov smo pri končni telesni višini ugotovili pomembno povečanje standardnega odklona višine od povprečja ($p < 0,01$), med skupinama ni bilo pomembne razlike. Večji zastoj telesne rasti je bil pri preiskovancih, ki so se zdravili v nižji starosti. V skupini preiskovancev, ki so prejeli večji odmerek profilaktičnega obsevanja, je bil zastoj rasti večji pri deklicah kot pri dečkih. Pri obeh skupinah preiskovancev smo ugotovili pomembno povečanje standardnega odklona ITM od povprečja od postavitve diagnoze do raziskave ($p < 0,0001$). Med skupinama ni bilo statistično pomembne razlike. Pri deklicah smo opažali zgodnejši nastop menarhe, vendar med skupinama ni bilo statistično pomembnih razlik.*

Zaključki *Pri bolnikih, ki so se zdravili zaradi ALL v otroštvu, smo ugotovili pomembno zmanjšanje končne telesne višine in povečanje ITM neodvisno od odmerka profilaktičnega obsevanja. Zdravljenje s citostatiki in obsevanje z ionizirajočimi žarki lahko vplivata na zastoj telesne rasti, povečanje telesne mase in pubertetni razvoj.*

Introduction

Acute lymphoblastic leukemia is the most common malignant disease in childhood. The development of intensified chemotherapy in combination with prophylactic cranial irradiation (CI) has greatly improved the survival rate. With increasing number of long-term survivors of childhood leukemia the late sequelae of treatment became apparent. Several follow-up investigations have shown a moderate reduction in final height. CI may cause pituitary dysfunction, of which growth hormone insufficiency is the most common endocrinopathy. Pituitary dysfunction is related to both the dose of irradiation and the method of fractionation. In most studies a greater loss of height was seen in the children who had received the higher dose of CI (1–3). Early and precocious puberty has been described in children after CI therapy in both low dose (18–24 Gy) given for CNS prophylaxis in leukemia (3, 4) and in higher doses (35 Gy or more) applied for brain tumors (5). Premature activation of the hypothalamic-pituitary-gonadal axis occurs as a consequence of hypothalamic dysfunction. Precocious and premature puberty in children treated for ALL may be an important factor in contributing to short stature. Age at onset of puberty seems to be directly correlated with age of treatment (4, 6, 7) and indirectly with body mass index (BMI) (6–8).

Sainsbury was the first who confirmed the impression that ALL survivors tend to be overweight. Weight gain was excessive. It started during treatment and persisted until eight years or more after diagnosis (9, 10). Nearly half of the group were still obese at final height (11). There is no significant difference in incidence of obesity between the sexes (10–12), but some studies provided the evidence that obesity in ALL survivors is mainly the problem in girls (13, 14). Most studies explain weight gain by CI (11, 13, 14). Other studies showed that corticosteroid therapy, in particular protocols with dexamethasone, are associated with obesity as an early and late side effect of antileukemic therapy (10, 12).

The aim of this study was to compare the effects of different doses of prophylactic cranial irradiation on growth, BMI and age of menarche in a cohort of survivors of childhood ALL who attained final height.

The study was conducted in accordance with the Helsinki Declaration and approved by the Medical Ethics Committee.

Patients and methods

The study included 47 patients (18 boys) who had been treated for childhood ALL at the University Children's Hospital in Ljubljana, Slovenia between 1976 and 1992. The data were analysed retrospectively from the patient's hospital records. The clinical evaluation (height, weight, pubertal stage) and endocrinological evaluation was performed on average 12.44 (3.6, range 5.0–23.2) years after diagnosis.

All patients received combination chemotherapy following chemotherapeutic protocols BFM 83, BFM 86 and BFM 93 that has been used at that time, 5 with induction therapy with prednisolone, asparaginase, vincristine as well as maintenance therapy with 6-mercaptopurine, methotrexate, and pulses of prednisone and vincristine. Central nervous system prophylaxis included cranial radiotherapy. Twenty-eight patients received lower doses (12–18 Gy) and 15 higher doses (20–30 Gy) of CI. Four patient had no radiotherapy. None had received gonadal or spinal irradiation. Children who had received any form of endocrine treatment were excluded from the study.

All the patients were in continuos first remission. Those with relapse of the disease were excluded from the study except two girls in whom relapse occurred after their final height was attained.

Growth and weight data were collected retrospectively from hospital records including height and weight obtained at diagnosis, end of treatment and final height. Height was measured with Harpenden stadiometer and expressed as SD score based on chronological age to allow for comparison of patients of different sex and age. Data were compared to the Tanner-Whitehouse growth charts (15). The SDS score was calculated by subtracting the population means for the child of the same age from the observed measurement for a child and dividing by the SD for the population. For a normally distributed population the mean SD score is zero and a score between –2 and +2 includes 95.44% of population. The change in height SDS for each patient was calculated by subtracting the SDS at final height from that at diagnosis. Final height was considered to be reached when the growth during the preceding year was less than 1 cm. Target height was calculated from mid-parental heights (16, 17).

Because of retrospective design pubertal growth and development could not be evaluated. Menarche was used as the most reliably recorded measure of puberty.

Body mass index (BMI) was used as an index of fatness according to the formula weight (kg)/(height)^2 (m^2). The BMI Z scores for each patient at diagnosis, at the end of the therapy and at final height were calculated with the reference to the French population standards published by Rolland-Cachera et al. (18). To establish the proportion of children with obesity, all patients having BMI SDS greater than 1.28 (above the 90th percentile) were considered obese.

Demographic data were expressed as means (± SD). Comparisons of changes in height and weight SDS for each patient at diagnosis and final height and between groups were made using paired and unpaired t-test.

Pearson's correlation coefficient was used to assess the effect of age at diagnosis on final height and menarche.

Results

Growth

Patient characteristics and baseline growth data, grouped according to the type of CNS prophylaxis received are summarized in the Table 1.

Table 1. *ALL survivors: patient and treatment characteristics.*

Razpr. 1. *Preživeli preiskovanci po zdravljenju ALL: značilnosti bolnikov in način zdravljenja.*

Th group Skupina	n	F/M	Age (dg.) yrs. Starost ob diagnozi (leta)	Age (f. h.) yrs. Starost – leta
No CI	4	2/2	7.2	17.1
12–18 Gy	28	16/12	5.4	17.0
20–30 Gy	15	11/4	5.0	19.7

The mean height at diagnosis in the treatment groups was not significantly different (height SDS 0.61 ± 1.17 vs. 0.5 ± 0.92, 18 Gy vs. 24 Gy, p = NS). Significant loses in individual height SDS from diagnosis to final height were noted in a group as a whole and also in both cranial irradiation treatment groups (–1.02 ± 1.0 [p < 0.01], –1.0 ± 0.84, 18 Gy [p < 0.01], –1.3 ± 1.2, 24 Gy [p < 0.01]). Irradiated patients had a greater loss in

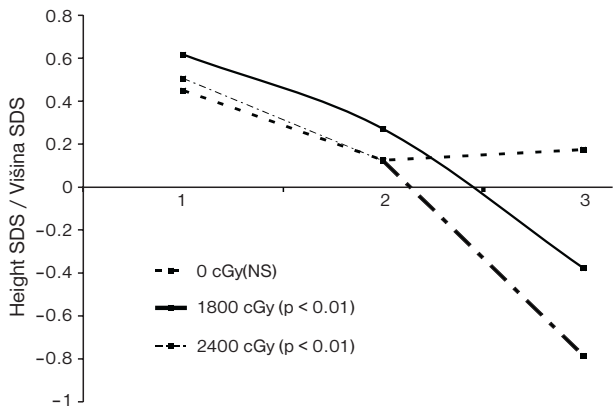

Figure 1. *Change in mean height SDS of patients grouped according to treatment regimen at diagnosis (1), the end of the treatment (2), at final height (3).*

Sl. 1. *Standardni odkloni telesne višine pri bolnikih, zdravljenih zaradi ALL v otroštvu, glede na odmerek profilaktičnega obsevanja (SDS telesne višine ob diagnozi [1], ob koncu zdravljenja [2], ob končni višini [3]).*

height SDS compared to nonirradiated patients. The patients treated with higher irradiation dose had a greater decrease in final height compared to those treated with lower dose but the difference did not achieve statistical significance (p = 0.2) (Figure 1).
With analysis of the group as a whole both younger age at the treatment and female sex were significantly associated with an overall decrease in height SDS. When we analyzed separate groups, the difference didn't reach significance.
At the time of diagnosis none of the patients had height more than 2 SD below the mean for population norms. Final heights were more than 2 SD below mean values in 3 subjects (6.6%), of whom 1 was treated with 18 Gy and 2 with 24 Gy prophylactic CI.
Final height SDS in relation to midparental height (MPH) SDS has been assessed in 37 patients of which MPH data were available. Average MPH was 167.5 ± 8.26 cm (SD, range 155.1–183.4). Thirteen individuals (35.1%) reached their MPH at final height, all (3/3) in nonirradiated group, 5/21 (23.8%) in 18 Gy and 5/13 (38.4%) in 24 Gy irradiation dose group. Twenty four (64.9%) patients hadn't reach their MPH at final height.

Puberty

Menarche was used as the most reliably recorded measure of puberty.
Table 2 shows the comparison between the 18 Gy and 24 Gy groups for age of menarche.

Table 2. *Menarche and cranial irradiation dose.*

Razpr. 2. *Starost ob nastopu menarhe glede na odmerek profilaktičnega obsevanja.*

Th group Skupina	n	Age at dg. yrs. Starost ob postavljeni diagnozi – leta	Menarche yrs. Menstruacija – leta	Sig.
Tanner	–	–	13.5	–
12–18 Gy	16	4.2	11.6	P < 0.01
20–30 Gy	11	4.7	11.5	P < 0.01

In a group as a whole menarche occurred between age 10 and 15 years. Menarche occurred significantly earlier in both irradiated groups compared to reference value (Tanner) (p < 0.001 for both dose groups), but there was no difference between both treatment groups (11.6±1.3 years vs. 11.4±1.1 years, 18 Gy vs. 24 Gy group, p = NS).
No correlation between age at diagnosis and age at menarche was found in any of CI treatment group (Pearson, NS).

Body mass index

For the group as a whole, there was a significant increase in BMI SDS from the time of diagnosis to final height (p < 0.001). The weight gain persisted throughout treatment and after treatment on till final height was reached (Figure 2). The difference between different CI dose treatment groups was not significant. Significant difference in mean BMI SDS between boys and girls was found only in 18 Gy CI treatment group (p < 0.05). The difference in the higher radiation dose

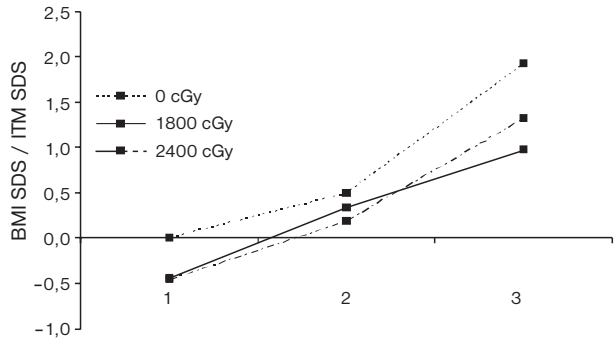

Figure 2. *Change in BMI SDS in patients treated for childhood ALL grouped according to treatment regimen (BMI SDS at diagnosis [1], at the end of the treatment [2], at final height [3]).*

Sl. 2. *Standardni odkloni ITM pri bolnikih, zdravljenih zaradi ALL v otroštvu, glede na odmerek profilaktičnega obsevanja (ITM SDS ob diagnozi [1], ob koncu zdravljenja [2], ob končni višini [3]).*

group was not significant, most probably because the number of boys was too small.
We could observe marked increase in prevalence of obesity in survivors of childhood ALL from 12.7% at diagnosis to 53.2% at final height.

Discussion

Growth failure has been observed in long-term survivors of childhood ALL.
Both Uruena et al. and Sklar et al. have conducted long-term growth evaluations that have included comparison analyses of patients who received 18 Gy and 24 Gy cranial irradiation. The former study showed similar reductions in height SDS for both groups of patients (4); the latter demonstrated that patients who received 24 Gy had more growth impairment than those receiving 18 Gy (2).
In our study we also observed significant decrease in HSDS from diagnosis to final height in both irradiation groups. Our results are in accordance with those of Sklar although the difference between the groups was not significant. Katz et al. compared the final height in a large group of patients treated for childhood ALL with high dose or no CI. They found that cranial irradiation was strongly associated with final height (19). There was a uniform trend of patients treated at an earlier age to have a greater reduction in final height (2, 19) which showed that age at irradiation is a critical factor in the onset of GH deficiency. It may be that the youngest at the time of irradiation are more vulnerable to irradiation-induced damage to the hypothalamic-pituitary axis (2, 5, 19).
Partial or complete growth hormone deficiency and growth impairment is well described after high dose CI for brain tumors distant from hypothalamic-pituitary axis (5, 20). It has been also noted after prophylactic cranial irradiation for childhood ALL with either 18 Gy or 24 Gy (3). Growth hormone insufficiency combined with early or premature puberty has

been recognized as a main factor of growth impairment after treatment of childhood ALL (4, 6). The analysis showed that CNS irradiation mostly affects the pubertal growth period (4, 7, 21). The spontaneous GH secretion was normal prepubertally but the analysis revealed an inability to respond to the increased demands during puberty (21).

Chemotherapy may also play a role in growth impairment. In children treated for ALL with chemotherapy without CI the chemotherapy exerted a negative influence on growth, but catch-up growth occurred within 2 years after cessation of therapy resulting in normal final height and body proportions (22). Different studies showed that patients who had received more intensive chemotherapy with the same dose of CI had bigger decrement in height SDS (23). Growth velocity was significantly lower in patients who were treated for more than 2 years or who had the more intensive chemotherapeutic protocol (24).

The multiagent chemotherapy during continuation treatment was followed by a continuous loss in height and resulted in a reduced final height. The authors assumed that chemotherapy might have direct effect on the large number of epiphyseal growth plates in the spine, or that it may impair the production of insulin-like growth factor-1 (IGF-1) by the liver (25).

Cranial irradiation and combination chemotherapy does not cause only significant loss of standing height, but it may also result in significant body disproportion with relatively short spine. In the study of Davies eighty one percent of those children in whom sitting height was measured had relatively shorter backs than legs and in nearly a quarter this proportion was markedly significant (26). At least in some children, much if not all of height loss after treatment for ALL is due to loss of sitting height. Possible explanations for this body disproportion include a disturbance of puberty or an effect of chemotherapy on epiphysial growth plate of the spine, or both. To diagnose severe growth hormone deficiency in childhood and young adult life, it has been suggested that a single estimate of the serum IGF-1 and IGFBP-3 concentrations provides an excellent screening investigation (27). Sklar et al. assessed the IGF-1 and IGFBP-3 concentrations in children with irradiation induced GH deficiency and found that IGFBP-3 levels were discordant with results of GH testing in 60% of subjects (28). In the young adult ALL study of Brennan et al. IGF-1 and IGFBP-3 estimations proved equally unhelpful in the diagnosing of severe GH deficiency (29).

Several reports had shown that early puberty in children with ALL might be another factor resulting in reduced final height (3, 4). Growth hormone insufficiency combined with early or premature puberty has been recognized as a main factor of growth impairment after cranial irradiation treatment of childhood ALL (4, 6, 7). Early and precocious puberty have been described in children following high-dose central nervous system radiation therapy for brain tumors. Puberty started significantly earlier in girls (8). A significant correlation exists between age at diagnosis and age of onset of puberty in boys and girls (8). Early activation of the hypothalamic-pituitary-gonadal axis may occur as a result of high as well as low dose CI. The growth of children with central precocious puberty is compromised by rapid epiphyseal maturation that ultimately limits growth.

The prevalence of obesity at final height indicates that considerable proportion of survivors of childhood ALL are overweight. An increased weight gaining velocity during and after treatment for childhood ALL has been observed in different studies (9–14).

Odame et al. have demonstrated that there is an increased prevalence in obesity in female survivors of ALL with 57% having BMI SDS greater than + 2 SD at four years follow-up compared with 21% of boys (13). Warner et al. also found higher prevalence of obesity in female survivors of ALL compared to girls treated for other malignancies and healthy controls represented by siblings (14).

Different factors have been suggested to contribute to excessive weight gain in these patients. Most studies explain weight gain by CI. It has been suggested that CI may cause damage to the hypothalamic-pituitary axis, inducing a decrease in growth and lipolysis which may result in obesity (13). Recent study suggest that leptin receptor gene polymorphism may influence obesity in female survivors of childhood ALL, particularly those exposed to cranial radiation (30). In contrast, the study of Van Dongen-Melman clearly demonstrated that protocols with CI did not induce more weight than those without CI (10). Protocols with the highest prevalence of obesity at follow-up were those with corticosteroids without CI. Some studies implied that the use of corticosteroid therapy has more dominant effect on weight gain than irradiation-induced pituitary dysfunction. The studies of Van Dongen-Melman and Groot-Loonen et al. showed that corticosteroids, in particular protocols with dexamethasone, were associated with obesity as an early and late side effect (10, 12). It remains unclear why the increase in weight continues long after treatment is stopped. In our cohort only 3 patients has been treated with protocols with dexamethasone. The number was to small to allow any statistical analysis.

Reductions in energy expenditure in childhood ALL survivors was found in study of Warner et al. The finding suggests that increased adiposity is associated with less energy expenditure caused by impaired exercise capacity as a consequence of chemotherapy and radiotherapy induced cardiorespiratory impairment (31). Reduction in a pulmonary function as a result of fibrosis caused by cyclophosphamide and bleomycin (32) and cardiotoxicity caused by antracyclines (33) may be the factors that contribute to reduced exercise capacity. Children treated for ALL are predisposed to excess weight gain and subsequent kobesity, by reduced total energy expenditure secondary to reduced habitual physical activity (34, 35). Lower energy expenditure during physical activity was associated prospectively with higher rates of excess weight gain.

Survivors of childhood cancer have been reported to have an sevenfold-increased risk for death from car-

diovascular diseases because of different manifestations of the metabolic syndrome. Obesity is one of the major factors contributing to the development of hypertension, insulin resistance, glucose intolerance or diabetes and dyslipidemia (36). Insufficient growth hormone secretion may contribute to low HDL holesterol and high triglyceride levels.

Weight control and regular physical exercise should be recommended in the follow-up of survivors of childhood ALL to reduce the risk of early manifestations of the metabolic syndrome.

Endocrinological investigations, fat distribution, body composition, energy expenditure, cardiac and lung function should be performed to further elucidate the etiological mechanisms for this late effect of ALL treatment.

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