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Longitudinal growth and final height in long-term survivors of childhood leukaemia

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Abstract Survival of children with acute lymphoblastic leukaemia (ALL) has increased considerably in recent years and data on the spontaneous growth and final height of these children are conflicting. Therefore, we analysed the longitudinal growth and final height in 52 survivors (33 females, 19 males) of childhood ALL. These children were diagnosed and treated in a single institution, all remained in first remission and were submitted to cranial irradiation with either 2400 or 1800 cGy. None of the patients received testicular or spinal irradiation. Median age at diagnosis was 4.2 (range 1.3–9.6) years in the first group (2400 cGy) and 3.9 (0.8–10.5) years in the second (1800 cGy). Standing height was measured at diagnosis, at the end of treatment (median 3.1 years after diagnosis), 6, 12, 24 months after the end of treatment, and finally at the completion of growth. In girls a significant decrease of mean height standard deviation score (SDS) during treatment and a catch up in growth after the end of therapy was followed by a second period of reduced growth. Mean final height SDS was significantly lower than the value at diagnosis in both groups of girls, but only in males treated with 2400 cGy. Mean overall loss in height SDS from diagnosis to final heigth was higher in females (−1.24) than in males (−0.40) (P = 0.009). Females ≤ 4 years of age at diagnosis showed a higher loss in final height than females > 4 years. An unchanged or improved final height was evident in 8 cases, the other 44 cases showed a final height decrease between −0.1 and −2 SDS in 36 and > −2 SDS in 8, 6 of whom were females ≤ 4 years at diagnosis and only 1 a female > 4 years. Only females treated at a younger age showed a final height lower than mid-parental height (−5.7 ± 1.8 cm, $P <$ 0.01), particularly those treated with 2400 cGy (−7.5 ± 2.5 cm, $P < 0.05$). Menarche occurred earlier than in the normal population (11.5 ± 1.2 years) with no differences between the two radiation dosages.

Conclusion Females, notably young girls, treated for ALL show a greater decrease in the final height than treated males. Early sexual maturation may contribute to the decrease in the final height. A better growth pattern seems to be shown by patients irradiated with the lower dosage.

Key words Final height · Acute lymphoblastic leukaemia

Abbreviations *ALL* acute lymphoblastic leukaemia · *GH* growth hormone · *SDS* standard deviation score · *TH* target height

Introduction

Several studies of children treated for acute lymphoblastic leukaemia (ALL) have focused on growth retardation due to the disease and its treatment [10, 18, 26]. While Clayton et al. [7] unequivocally demonstrated the effect of chemotherapy on growth, others indicated an important role of radiation demonstrating a better growth of children treated without prophylactic cranial irradiation [9, 14] and a different growth pattern depending on the number of fractions of the radiation regimen [2]. In recent years prophylactic cranial irradiation has been safely reduced from 2400 cGy to 1800 cGy [16] and the effect on growth of the lower dosage has been the subject of several studies. While some papers reported a comparable growth independent of radiation dosage [22, 27], others indicated a lesser growth retardation in children treated with 1800 cGy [4]. However, in these studies growth was followed for only few years after the end of therapy, and the results cannot be considered as definitive.

Recently some studies have focused on the final height of ALL [19, 21, 25] but the data are still conflicting.

In this study we have analysed the longitudinal growth of 52 patients treated with two irradiation dose regimens (1800 and 2400 cGy) for childhood ALL who had completed their growth.

Patients and methods

Patients

Data were reviewed for long-term survivors of ALL treated at the third Paediatric Clinic of the University of Bologna who remained in complete remission and had completed their growth. None had received spinal or gonadal irradiation, or had been treated with growth hormone (GH) and all had a normal, spontaneous puberty. Patients with dysmorphic syndromes, abnormal karyotypes or incomplete data were excluded. Data from 52 patients were analysed (19 males and 33 females). Age at diagnosis ranged from 0.8 to 10.5 years (median age 4.2 years). All patients were treated with chemotherapy according to the protocols of the Italian Society for Paediatric Haematology and Oncology [17]. They all received prophylactic cranial irradiation: 31 patients (14 males and 17 females) were treated with 2400 cGy (12 fractions of 200 cGy each) and 21 (5 males and 16 females) with 1800 cGy (10 fraction of 180 cGy each). Age at diagnosis ranged in the first group (2400 cGy) from 1.3 to 9.6 years (median age, 4.2 years) and in the second group (1800 cGy) from 0.8 to 10.5 years (median age 3.9 years).

Methods

The standing heights were obtained retrospectively at diagnosis (at the start of treatment), at the end of treatment (at a median chronological age of 7.4 years, range 3.8–12.8 years, and from 2 to 4 years (median 3.1 years) after diagnosis), 6, 12 and 24 months after the end of treatment, and finally at the completion of growth.

Patients were considered to have reached final height if their height increased less than 1.0 cm over a 1 year period of observation or when their age was over 18 years in girls and over 21 years in males.

Height was measured by experienced staff in the morning with a wall stadiometer (Harpenden Ltd, Crymmych, Pembrokshire, Wales). Stature was expressed as SDS from the following formula $(X - \bar{X}/SD)$ where X is the measurement, $\bar{X}$ is the mean measurement of a standardized group for the age in question, and SD is standard deviation of the group. Normal standards from Tanner et al. [23, 24] were used. No adjustment was made for secular trend in height. Parents height of 48 patients was measured and the target height (TH) was calculated according to the formula: TH for boys = (mothers's height + father's height)/2 + 6.5 cm; TH for girls = (mother's height + father's height)/2 – 6.5 cm.

Age at menarche was registered in 31 females and normal data from Marshall and Tanner [12] were used for comparison.

Statistical analysis

For statistical analysis, the computer program Statistical Package for Social Sciences was used. Changes in the height SDS, dating from diagnosis, were assessed by multivariate analysis of variance for repeated measurements.

Statistical comparisons were made by Student's t-test and χ^2 analysis. Pearson correlation coefficient was also calculated and paired t-test was used to determine whether the change observed within individuals SDS between two periods was significant. Data are expressed as means ± SEM, except as noted.

Results

The mean (± SEM) standing height SDS at the various examinations are shown in Fig. 1. A significant decrease in mean height SD during the treatment and a catch-up in growth after the end of therapy was evident in females. In this group multivariate analysis of variance for repeated measurements showed a significant difference in SDS at the different observations ($F = 14.4$, $P < 0.0001$) (Fig. 1). Two years after the end of therapy the mean height SDS was similar to that at diagnosis, but final height was again significantly reduced compared to the value at diagnosis. Final

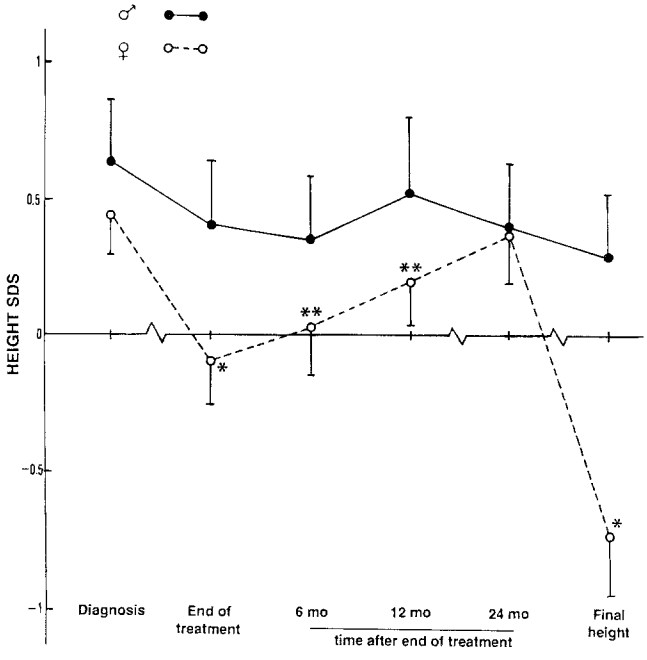

Fig. 1 Mean (± SEM) SD score for height of patients (19 males and 33 females); significance compared to value at diagnosis is shown (*$P < 0.001$; ** $P = 0.05$)

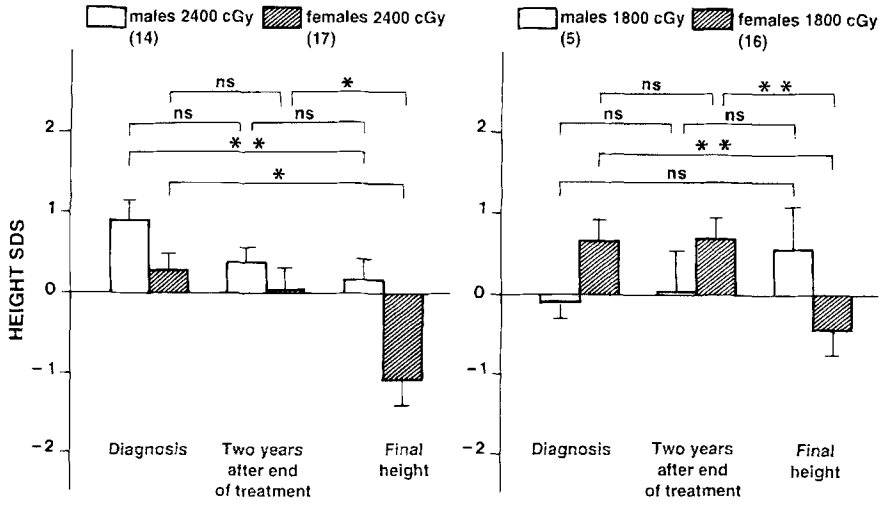

Fig. 2 Change in mean (± SEM) height SDS according to sex and treatment regimen (* $P < 0.001$; ** $P < 0.005$)

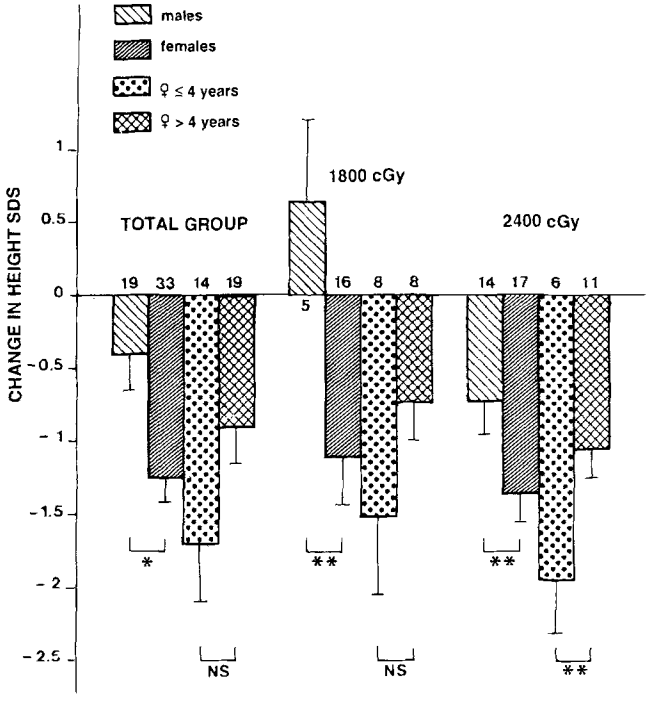

Fig. 3 Overall loss in height SDS (mean ± SEM) from diagnosis to final height (* $P = 0.009$; ** $P < 0.05$)

height SDSs were significantly lower than those values at diagnosis in both groups of females divided according to the radiation dosage, but only in males treated with 2400 cGy (Fig. 2). The overall loss in height SDS from diagnosis to final height was constantly and significantly higher in females than in males (total group: −1.24 ± 0.18 vs −0.40 ± 0.24, $P = 0.009$) independent of radiation dosage (group 2400 cGy: −1.36 ± 0.2 vs −0.72 ± 0.2, $P < 0.05$; group 1800 cGy: −1.11 ± 0.32 vs 0.64 ± 0.57, $P < 0.05$) (Fig. 3). Females who were ≤ 4 years at diagnosis showed a higher loss in final height compared to females older than 4 years, the difference however was significant only for the 2400 cGy group (2400 cGy group: −1.92 ± 0.37 vs −1.05 ± 0.19, $P < 0.05$; 1800 cGy group: −1.51 ± 0.56 vs −0.72 ± 0.28, $P = 0.22$) (Fig. 3). Males did not show any significant difference of final height dependent on age at diagnosis.

Taking into consideration the total group of patients (52 subjects) only 8 cases showed a final height SDS that was unchanged or improved compared to the value at diagnosis (5/19 males and 3/33 females; 7/21 in the 1800 cGy group and 1/31 in the 2400 cGy, $P = 0.01$), the other 44 cases showed a final height decrease between −0.1 and −2 SDS in 36 (13/19 males and 23/33 females) and >−2 SDS in 8 (1/19 males and 7/33 females).

Females ≤ 4 years at the time of diagnosis (14 cases, 6 treated with 2400 cGy and 8 with 1800 cGy) showed a final height SDS decrease > −2 SDS in 6 cases versus only 1 case ($P < 0.05$) among the 19 females > 4 years at diagnosis (11 treated with 2400 cGy and 8 with 1800 cGy).

Midparental height was higher than patients final height only in females with a younger age at diagnosis (−5.7 ± 1.8 cm, $P < 0.01$) particularly in those treated with 2400 cGy (−7.5 ± 2.5 cm, $P < 0.05$) (Table 1).

Age at menarche was registered in 31 girls and it occurred earlier than in the normal population at a mean age (± SD) of 11.5 ± 1.2 years with no difference between the two radiation dosages (2400 cGy: 11.6 ± 1.6 years, 1800 cGy: 11.5 ± 0.7 years) (Fig. 4).

A correlation was found between height loss from diagnosis to the end of chemotherapy and height loss from diagnosis to final height ($r = 0.65$; $P < 0.0001$).

Discussion

Patients treated for ALL presented growth retardation during chemotherapy followed by a period of improved growth after treatment was stopped. The period of catch-up growth may be missed if patients' height is not monitored during this phase but only at the end of growth as in the recent study by Sklar et al. [21].

In our patients catch-up growth in females was followed by a second period of marked decrease in height SDS start-

Table 1 Comparison between patients' target and final heights (mean values ± SD)

		Total group	2400 cGy	1800 cGy	≤4 years	>4 years	≤4 years 2400 cGy
Males	Patients No.	17	13	4	8	9	7
	Target height	175.0 ± 1.0	175.0 ± 1.0	174.7 ± 3.3	176.1 ± 1.5	174.0 ± 1.5	175.1 ± 1.2
	Final height	176.3 ± 0.8	175.7 ± 1.6	178.2 ± 3.6	177.6 ± 1.7	175.2 ± 2.4	176.6 ± 1.6
	Difference	+1.3 ± 0.8*[3]	+0.71 ± 0.9	+3.5 ± 1.6	+1.5 ± 0.7*[4]	+1.2 ± 1.5	+1.5 ± 0.9*[5]
Females	Patients No.	31	15	16	14	17	6
	Target height	159.0 ± 1.0	157.4 ± 1.3	160.5 ± 1.5	160.6 ± 1.7*[1]	157.7 ± 1.2	159.9 ± 2.4*[2]
	Final height	156.7 ± 1.3	155.3 ± 2.0	158.0 ± 1.7	154.9 ± 2.5*[1]	158.2 ± 1.1	152.4 ± 4.3*[2]
	Difference	−2.3 ± 1.2*[3]	−2.1 ± 1.9	−2.5 ± 1.6	−5.7 ± 1.8*[4,6]	+0.5 ± 1.4*[6]	−7.5 ± 2.5*[5]

*[1] $P < 0.01$, *[2] $P < 0.05$ for the difference between target and final height
*[3] $P < 0.05$, *[4] $P < 0.005$, *[5] $P < 0.05$ for the difference between males and females
*[6] $P < 0.01$ for the difference between females ≤4 years and >4 years

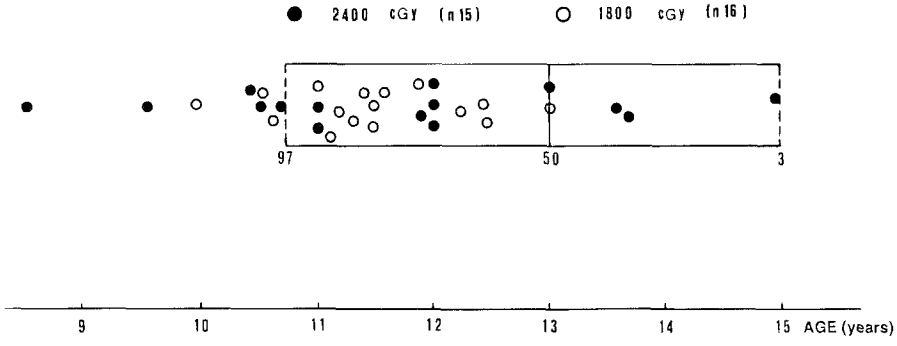

Fig. 4 Age at menarche of 31 girls. The percentile of a normal population from Marshall and Tanner [12] are shown

ing 2 years after cessation of therapy. Therefore a follow up limited to the first years after completion of chemotherapy may lead to underestimates of the real impact of treatment of leukaemia on growth of long-term survivors [1, 20, 26].

The deceleration in growth during the period of the pharmacological treatment has been attributed both to chemotherapy and to cranial irradiation [2, 7, 14, 21]. Patients who received chemotherapy for 2 or 3 years showed a catch-up growth in the 3rd or 4th year after diagnosis irrespective of the radiation schedule [7]. On the other hand patients who had not been treated with cranial irradiation showed a smaller decrease in height SDS during chemotherapy [2]. The highly significant correlation between height decrease at the end of therapy and the final height decrement suggests a possible role on adult height not only of cranial irradiation but also of chemotherapy.

The second period of deceleration of growth observed by us [4] and others [13, 19, 25] may be related to the GH insufficiency caused by irradiation administered to the hypothalamic-pituitary region [4, 6, 15].

It has recently been suggested that in irradiated patients the relatively small amount of GH could be sufficient for prepubertal but not for pubertal growth [5, 8, 15]. Impaired pubertal growth has been reported in girls treated for ALL by Möell et al. [15] and in both sexes by Uruena et al. [25].

Therefore the deceleration in growth in our females in the period between 2 years after the end of therapy and the completion of growth may be due to an attenuated pubertal growth. A tendency towards precocious or early pubertal development in long-term survivors of ALL who were treated with cranial irradiation has been reported [11, 15, 25]. This is in accordance with our observation that mean age at menarche was earlier in girls compared to the criteria of Marshall and Tanner [12] and above the 97th percentile in 8 cases. Early puberty in females may be a contributory factor to the decrease in final height and it could explain why growth impairment was greater in girls than in boys.

While Uruena et al. [25] found the reduction in final height to be independent from the cranial irradiation dosage (2400 cGy or 1800 cGy), Sklar et al. [21] observed a greater growth impairment in patients treated with the higher dose regimen. Among our patients normal growth occurred in 7/21 of the 1800 cGy group but only in 1/31 of the 2400 cGy ($P = 0.01$). Males treated with 1800 cGy did not show any decrease of the final height compared to the value at diagnosis. Females treated with 2400 cGy showed a higher final height decrease than that observed in the lower radiation group (−1.36 vs −1.11); the difference however was not significant and this probably reflects the relatively small number of patients studied. As reported by others [21, 25] growth retardation was more pronounced in girls treated at a younger age. In our patients this phenomenon was evident in both dose regimens but it was significant only in girls treated with 2400 cGy. The higher decre-

ment in final height of younger children may be related to a greater susceptibility of the hypothalamo-pituitary region to radiation damage as evidenced by a smaller pituitary dimension [5] and a more evident subnormal GH release [3] in children irradiated at a younger age.

The comparison of midparental height with patients' final height, even though no adjustement was made for secular trend in height, confirmed the prevalent growth impairment of young females (–5.7 cm), particularlay of those treated with 2400 cGy (–7.5 cm).

In conclusion our data suggest the following considerations: after the end of therapy children treated for ALL normally show a satisfactory growth rate and this could lead to the mistaken assumption that final height will be normal. However, a reduced pubertal growth spurt may be associated with an early sexual maturation and cause an important decrement in the final height. This is more evident in girls than in boys, particularly those treated at a young age. The number of patients studied is too small to draw any definitive conclusion on the different effects of the two radiation regimens on final height. A better growth pattern however seems shown by patients irradiated with the lower dosage.

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