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Factors Contributing to the Impairment of Growth in Children with Acute Lymphoblastic Leukemia

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Abstract. Growth was studied in 88 long-term survivors of acute lymphoblastic leukemia who had been treated with three different regimens of therapy. The following time periods were evaluated: (1) during therapy; (2) between the end of therapy and the onset of puberty, and (3) between the onset of puberty and the most recent observation. We found: (1) a reduction of height SDS during therapy, related to the irradiation dose used; no significant effect of the duration of the therapy could be established; (2) a normal growth rate during the second time period studied for the total group, but a further decrease in height SDS for those found to be growth hormone deficient after therapy (47%), and (3) a further decrease in height SDS during puberty. The timing of puberty in the female patients was normal. We conclude that in patients treated for acute lymphoblastic leukemia, growth impairment has several components, different in timing and mechanism.

Introduction

Several studies have been published concerning growth failure during long-term follow-up of acute lymphoblastic leukemia (ALL) patients treated with combination chemotherapy and prophylactic cranial irradiation. The results are conflicting both in terms of the importance of growth failure and the occurrence of growth hormone (GH) deficiency [1–10]. Although the pubertal growth spurt seems to be impaired, few data have been reported in these patients [11–13]. In this study we have evaluated height from the time of diagnosis of ALL until final height, with emphasis on the pubertal period. We attempted to further elucidate which factors are responsible for growth failure and what is the mechanism involved.

Patients and Methods

From 1976 to 1983, 140 children with ALL were diagnosed at the State University of Ghent, Paediatric Department. They were treated with three different therapy regimens, differing by their duration of chemotherapy and irradiation dose used. Between 1976 and 1981, the EORTC-ALL-58-71 protocol [14] was used, this included a 5-year treatment and an irradiation dose of 2,400 cGy. Between 1981 and 1983 a 3-year protocol was used, EORTC-pilot study BFM 58-81 [15], the irradiation dose depended on a calculated risk factor (including the size of liver and spleen and the number of lymphoblasts). The high risk group received 2,400 cGy in contrast to 1,800 cGy for the low risk group. From 1983 the EORTC-ALL-58-83 protocol with a 2-year duration has been used, the irradiation dose depending on the risk factor. The high risk group received 2,400 cGy after randomization. The fractionation dose was 200 cGy in each protocol. Intrathecal methotrexate was used in each protocol and more recently high dose intravenous methotrexate in association with the intrathecal doses.

By 1988, 88 patients (43 m, 45 f) were in complete remission, 5–12 years after the time of diagnosis (mean 7.3 years). These patients were included in this study. Clinical data were reviewed at the following key times: diagnosis, end of therapy, onset of puberty, most recent observation for those in puberty and final height (n = 8). Height and weight were expressed as standard deviation score (SDS) according to the Tanner Standards [16]. Growth velocity for chronological age was calculated over 12 months according to the charts of Tanner [16]. In girls, the time of onset of breast development was noted and these data were expressed as SDS according to the standards of Marshall and Tanner [17].

GH secretion was evaluated during the insulin tolerance test (0.1 U/kg i.v.) and the glucagon test (0.1 mg/kg i.m.) [18]. This evaluation was performed more than 18 months after irradiation (mean 4.9 years). Serum GH was measured using the HGH-RIA-100 (Medgenix®) kit. The limit of detection was 0.08 ng/ml. The inter-assay and intra-assay coefficients of variation were 14 and 9% respectively. A response of < 10 ng/ml (20 mU/l) in both tests was defined as GH deficiency. Thyroid function was assessed by standard radioimmunoassays. The hypothalamo-pituitary-gonadal axis was evaluated using the GnRH stimulation test (25 μg/m² i.v.). The gonadotropins were measured by radioimmunoassay [19]. Linear regression, Student's t test and the Mann-Whitney U test were used in data analysis.

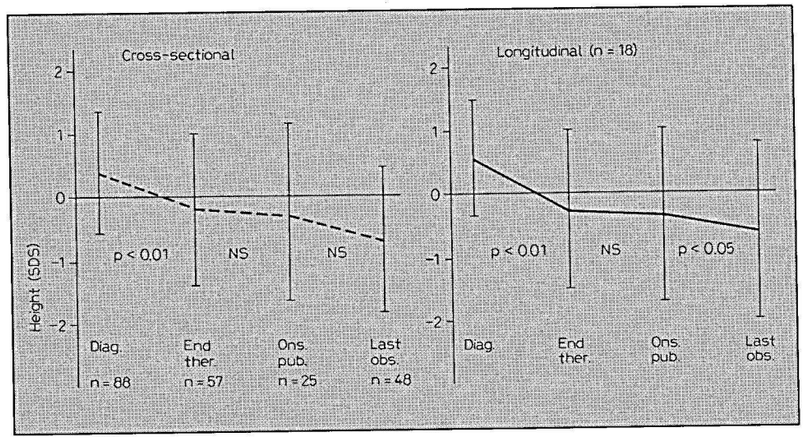

Fig. 1. Cross-sectional and longitudinal data of height SDS from the time of diagnosis until the last observation.

Results

Height in Relation to Time after Diagnosis

Eighty-eight patients (43 m, 45 f) were studied at different times after diagnosis. Forty-nine patients received the 5-year protocol, 20 the 3-year protocol and 19 the 2-year protocol. Twenty-six received 1,800 cGy and 43 received 2,400 cGy. Their mean ages at the different key times were 6.01 years at diagnosis (n = 88), 8.39 years at the end of therapy (n = 57), 11.16 years at the onset of puberty (n = 25) and 14.47 years at the most recent observation (n = 48), with mean height SDS being respectively 0.40 ± 0.96, −0.20 ± 1.21, −0.26 ± 1.4 and −0.70 ± 1.13 SD. Eighteen patients were followed longitudinally. Their height data were not different from those obtained in the cross-sectional study: mean height SDS was 0.54 ± 0.90 SD at the time of diagnosis, −0.28 ± 1.24 SD at the end of therapy, −0.36 ± 1.32 SD at the onset of puberty and −0.59 ± 1.37 SD at their most recent observation (fig. 1). Final height was achieved in 8 cases and was −0.67 (± 0.90 SD) SDS of height in contrast to their adult height predicted at the time of diagnosis which was 0.31 (± 0.93 SD) SDS ($p < 0.02$). Weight/length ratio was calculated and did not change significantly throughout the entire study.

Parameters of Therapy in Relation to Growth during Therapy

Irradiation dose: The difference in height SDS between diagnosis and the evaluation 5 years later was −1.16 ± 0.72 SD in the group receiving 2,400 cGy (n = 36) and −0.33 ± 0.75 SD in the 1,800-cGy group (n = 20). This difference is highly significant ($p < 0.01$) (fig. 2).

Duration of chemotherapy: The difference in SDS of height was −0.56 ± 0.74 SD in the group receiving 2 years' treatment (n = 9) and −1.06 ± 0.79 SD in the 5-year treatment group (n = 44). This difference is not significant possibly due to the small number of patients followed for 5 years in the 2-year protocol, which is the most recent one (fig. 2).

GH Secretion and Growth

GH secretion was evaluated in 34 patients with a height SDS not significantly different from that of the total group. Thyroid function was normal in all the patients. Sixteen patients (47%) were found to be GH deficient on two pharmacological tests. The reduction in height SDS during therapy was more marked ($p < 0.05$) in the deficient group (fig. 3a) than in the nondeficient group (−1.12 ± 0.63 versus −0.45 ± 0.61 SD). Between the end of therapy and the onset of puberty, we did not observe any significant decrease in height SDS in the total group (fig. 1); however, during the same period

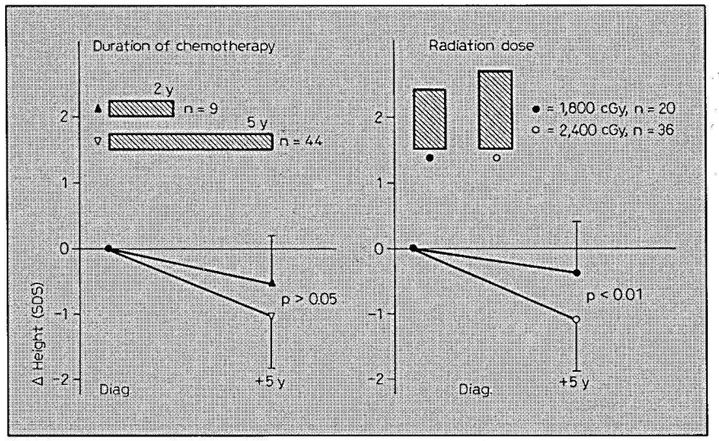

Fig. 2. Influence of duration of chemotherapy and irradiation dose on the change in height SDS between the time of diagnosis and the evaluation 5 years later.

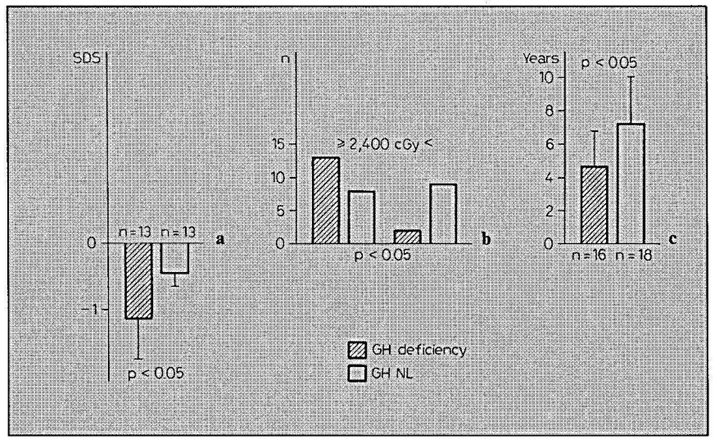

Fig. 3. a Loss of height SDS during therapy in GH-deficient and nondeficient patients. **b** Influence of the irradiation dose on the occurrence of GH deficiency. **c** GH status related to chronological age at the time of diagnosis.

there is a significant reduction ($p < 0.01$) of height SDS for the GH-deficient group (-0.84 ± 0.84 versus -1.54 ± 0.61 SD) as compared with the nondeficient group, who showed a slight increase of height SDS back to the pretreatment value (0.16 ± 1.50 versus 0.48 ± 1.52 SD) (fig. 4).

Among 16 GH-deficient patients, 13 (81%) had received 2,400 cGy compared with only 8 (44%) out of 18 in the nondeficient group ($p < 0.05$) (fig. 3b). In the GH-deficient group, mean age at diagnosis was significantly lower than in the group with normal GH secretion: 4.69 ± 1.98 versus 7.22 ± 2.73 years ($p < 0.05$) (fig. 3c). The responses of FSH and LH to GnRH were evaluated in the 34 patients and found to be normal according to their pubertal stage.

Puberty and Growth in Female ALL Patients

In figure 5 is shown height velocity from 2 years before the peak height velocity until 2 years after the peak. Data obtained in female ALL patients are compared with those of average maturers from a group of normal girls [17].

For the first 3 years of evaluation, height velocity is significantly lower in ALL patients. The overall gain for the 5-year period is 23.9 cm compared to 28.16 cm for the control group ($p < 0.05$). The time of onset of puberty evaluated in 30 female patients (mean age 11 ± 0.9 years) was not significantly different from normal girls. The reduction in height SDS between the time of diagnosis and the last observation was not correlated with the time of onset of puberty.

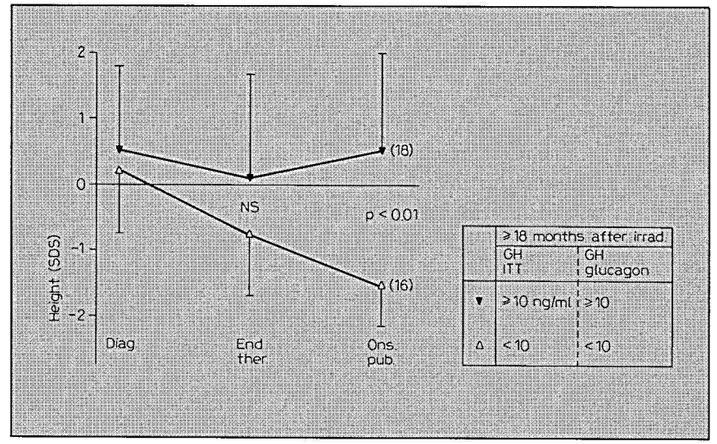

Fig. 4. Cumulative change in height SDS in GH-deficient and nondeficient patients during therapy and between the end of therapy and the onset of puberty.

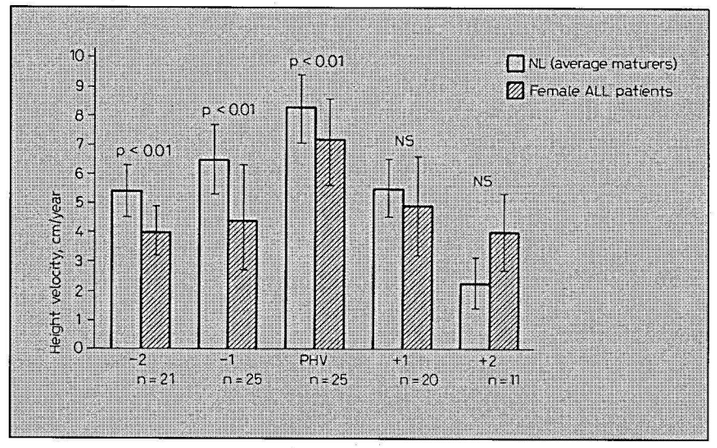

Fig. 5. Height velocity in female ALL patients compared to normal average maturing girls from 2 years before the peak height velocity (PHV) until 2 years after the peak.

Discussion

We have observed a similar pattern of change in height SDS in a longitudinal and a cross section study of ALL patients: (1) a reduction during therapy; (2) a steady state between the end of therapy and the onset of puberty, and (3) a further reduction during puberty.

The reduction of height SDS during therapy has been described by several authors [2, 3, 10, 20–23, 25] but not all [4, 8, 9, 24, 26]. We tried to clarify this by examining the influence of parameters of therapy such as duration of chemotherapy and irradiation dose on growth failure.

While the role of irradiation is usually emphasized, the role of chemotherapy has only been stressed recently [27, 28]. The great number of patients with growth failure in the study of Kirk et al. [27] might be due to the intensive chemotherapy protocol used, as the irradiation dose was the rather 'classical' dose of 2,400 cGy.

We found that patients receiving the highest irradiation dose had the most pronounced growth failure. This is related to the findings of Shalet et al. [7]. They reported that a higher irradiation dose is responsible for a greater proportion of GH-deficient patients. However, GH deficiency does not always result in growth failure since normal growth has been reported in patients with blunted GH responses to pharmacological stimuli [5]. Not only the total irradiation dose is important but also the fractionation dose which was identical in both groups of patients in our study.

Among our patients, 47% were found to be GH deficient. We used pharmacological tests to define GH deficiency. Blatt et al. [29] have suggested that 24-hour integrated GH secretion could be a more sensitive index of GH deficiency, but this has not been confirmed by others [30, 31]. Patients found to be GH deficient after therapy had already shown a greater reduction in height SDS during therapy. GH-deficient patients show a further decrease in height SDS between the end of therapy and the onset of puberty. This observation is in contrast to the nondeficient group, who showed a tendency to catch up. This is an important finding suggesting that a height velocity parallel to the normal standards after therapy should not be considered necessarily as normal and does not mean that GH deficiency is excluded. In agreement with Shalet et al. [6], most of the GH-deficient patients were among those who received the highest irradiation dose. We also confirmed the finding of Brauner et al. [32] that younger patients at diagnosis are more susceptible to radiation-induced GH deficiency.

Growth during puberty in female ALL patients off therapy has not been studied in detail until recently [11, 13, 33]. We do not confirm the finding of an early puberty reported by others [11, 13]. The growth spurt is clearly reduced, mainly during the first 3 years of pubertal growth. Moëll et al. [13] have suggested a possible inability of GH secretion to respond to increasing sex steroids during puberty. Certainly an early pubertal growth spurt can mask relative growth failure. This is the main reason for evaluating growth not only in terms of chronological age but also pubertal stage. In conclusion, our data confirm that factors resulting in growth failure in ALL patients include age at diagnosis, and therapeutic modalities and schedules. This study shows that deficiency in GH secretion is an important mechanism. The deficiency in GH secretion will affect growth differently in relation to the time period studied. Obvious reduction in height SDS occurs during therapy and puberty. Confusing growth data are obtained between the end of therapy and the onset of puberty, at which time the growth rate is apparently normal. However, this may not be normal in that catch-up growth should have occurred.

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Discussion

Ranke: Is the absence of catch-up growth after completion of chemotherapy for ALL an indication of an overall poor outcome of growth and could it be used to select whom to treat with GH?

Logghe: I showed that there is a further decrease in height SDS in the period between the end of chemotherapy and the onset of puberty in the group shown to be GH deficient. We think it is a very important observation that the impression of a 'normal' growth rate after chemotherapy may imply that growth is normal. However, this is not the case as catch-up growth should occur under normal circumstances.

Dacou-Voutetakis: A number of our ALL children have been followed to completion of growth with a mean height loss of -0.83 ± 1.16 in girls and -0.46 ± 1.0 in boys. Many of these children are obese, particularly the girls. A considerable number of the children have raised FSH and LH levels compatible with either primary gonadal damage or precocious puberty.

Logghe: GnRH tests were performed in all those patients who were tested for GH deficiency. All values obtained were in accordance with their pubertal stage. There were no patients who became obese during the entire study.

Stahnke: In support of two former remarks I would like to report on final adult height in 24 adults who had formerly been treated for ALL. Mean adult height in males was 180.0 ± 5.3 cm and in females 170.2 ± 6.6. Thus, no growth deficit was present. The differences from other studies may be due to different treatment schedules and protocols.

Logghe: I agree that the chemotherapy regimens and radiation schedules are very important in respect to final height.

Hesse: Adult height in 26 subjects treated for ALL or non-Hodgkin lymphoma is completely in the normal range of the population, that means 176 cm in males and 165 in females in a study, which was performed at the Children's Hospital of Jena, GDR. In comparison to parents' height there is a loss of 2–3 cm. These data underline that there is no indication to treat all patients with GH.

Logghe: We fully agree that biochemical evidence of GH deficiency in itself is not a reason to start replacement therapy. A careful follow-up of the growth data in these patients remains necessary.