Longitudinal Linear Growth and Final Height is Impaired in Childhood Acute Lymphoblastic Leukemia Survivors after Treatment without Cranial Irradiation

Els Vandecruys, MD1, Catharina Dhooge, MD, PhD1, Margarita Craen, MD2, Yves Benoit, MD, PhD1, and Jean De Schepper, MD, PhD2

Objective To evaluate long-term growth and final height (FH) in survivors of childhood acute lymphoblastic leukemia (ALL) who were treated without cranial radiation therapy and underwent evaluation of growth hormone (GH) status at the end of treatment.

Study design Data on longitudinal growth (collected at the start of treatment, end of treatment, and 1 year thereafter) and FH of 67 adult survivors of childhood ALL who had been treated according to European Organisation for Research and Treatment of Cancer 58831/2 protocols with chemotherapy as the only treatment modality were reviewed retrospectively. Height data were expressed as SDS for national references. The relative role of sex, age at diagnosis, intensity of chemotherapeutic regimen, and GH status at the end of treatment as contributing factors were analyzed.

Results A modest but significant loss in FH (change in SDS $\Delta$SDS = $-0.59 \pm 0.86$; $P < .001$) was found. Two-thirds of the height deficit observed from diagnosis until FH occurred during treatment. The height deficit was more severe in the male patients ($P = .036$). The $\Delta$SDS for height from diagnosis to FH was not correlated with age at diagnosis or intensity of treatment. No correlation was found between the results of the GH stimulation test and $\Delta$SDS for height from diagnosis or the end of treatment to FH.


Acute lymphoblastic leukemia (ALL) accounts for 25% of all cancer diagnoses made in children. The survival rate in ALL has improved markedly over the past 4 decades, with a 5-year survival rate of $\geq 90\%$ reported in recent trials.1 Impaired linear growth and reduction of adult final height (FH) are well-recognized complications of ALL treatment, including cranial radiation therapy (CRT).2-10

CRT was standard for treatment of subclinical central nervous system (CNS) involvement for all children during the 1970s and early 1980s. Since the early 1980s, prophylactic CRT has been increasingly replaced by intensified systemic and intrathecal (IT) chemotherapy, in most cases including methotrexate (MTX) given intravenously (IV) in intermediate or high doses simultaneously with IT MTX. The specific effect of chemotherapy on linear growth during the treatment of ALL without CRT has been studied3-5,7-11; however, the available data on long-term growth and FH remain scarce and conflicting, with some authors reporting no affect on FH4,8,11 but others reporting a significant decrease in FH4,9

In this study, we performed a retrospective review of statural growth and FH in 67 adult survivors of childhood ALL who underwent chemotherapy as the sole treatment modality out of a cohort of 76 patients treated in accordance with European Organisation for Research and Treatment of Cancer (EORTC) 58831 and 58832 protocols. In addition, the relative roles of sex, age at diagnosis, pubertal status at diagnosis, intensity of treatment, and growth hormone (GH) status at the end of the oncologic treatment as contributing factors were analyzed.

Methods

The original study group comprised 76 adult survivors in first complete remission of childhood ALL who had been diagnosed between August 1983 and July 1989 and treated at our center according to protocols 58831 (in children with standard-risk char-
acteristics) and 58832 (in children with medium- and high-risk characteristics) designed by the Children's Leukemia Cooperative Group of the EORTC. Patients with CNS manifestations at the time of diagnosis were not eligible for these trials, which were based on Berlin-Frankfurt-Münchener protocols. Detailed information on risk group definitions and treatments are available elsewhere. The 45 children with standard-risk ALL treated according to EORTC protocol 58831 compose group 1 in the present analysis; none of these children received CRT as part of CNS prophylaxis. Of the 31 children with medium- or high-risk ALL treated according to protocol EORTC 58832, 19 were randomized to receive or not receive CRT in addition to chemotherapy as CNS prophylaxis; the 9 patients who were randomized to receive CRT were excluded from this analysis. In 1988, randomization was stopped, CRT was omitted, and the subsequent protocol was pilot tested in our center, which resulted in the addition of high-dose cytarabine to the therapy of the last 12 patients treated according to EORTC protocol 58832. The 10 patients who were randomized without CRT and the 12 patients who did not receive CRT and received high-dose cytarabine composed group 2 in the present analysis.

In both protocols, the chemotherapeutic regimen applied was of moderate intensity according to the 3 categories as defined by Sklar et al, with the regimen used in EORTC protocol 58832 more intensive than that used in protocol 58831. In brief, all patients received a 5-week induction phase with prednisolone, vincristine, daunorubicin, asparaginase, and an IT dose of MTX, followed by a 4-week early consolidation phase with 6-mercaptopurine (6-MP), cytarabine, and MTX IT. Standard risk patients were randomized to receive or not receive cyclophosphamide 2 g/m², whereas all medium-risk and high-risk patients received this agent. Subsequently, standard-risk patients underwent interval therapy comprising an 8-week course of 6-MP and 4 courses of IV MTX 500 mg/m² and IT MTX instead of CRT as CNS prophylaxis. The medium-risk and high-risk patients underwent an 8-week course of 6-MP and 4 courses of IV MTX 2500 mg/m² and IT MTX; 12 patients also received high-dose cytarabine 8 g/m². Finally, standard-risk patients received a 4-week late intensification treatment with dexamethasone, vincristine, Adriamycin, asparaginase, 6-thioguanine, and cytarabine. For medium-risk and high-risk patients, this late intensification lasted 6 weeks and also included cyclophosphamide. Maintenance treatment consisted of 6-MP daily and oral MTX weekly, without IT treatment, for 2 years after the start of induction therapy.

**Methods**

This retrospective study was approved by the hospital's Ethical Review Board. Two variables were used to evaluate the growth outcome: FH SDS and ΔSDS for height between diagnosis and FH. Data for height and weight were obtained at diagnosis (ie, at the beginning of treatment), at the end of treatment, at 1 year after treatment, and at achievement of FH. All 67 patients were included in this longitudinal evaluation of linear growth from diagnosis until 1 year after the completion of treatment. In all patients, body mass index was calculated at the beginning and the end of treatment based on available body weight data. FH was defined as the height reached at chronological age 18 years in males and 16 years in females, or the height that increased <1 cm within the preceding 1-year period. Six patients were excluded from the evaluation of FH because of missing data.

Height was measured by the medical staff using a length board for infants and a scale-mounted stadiometer for older children and adults. Data are expressed as SDS, reflecting the deviation of height measurements from the standard normal population mean (SDS = 0). SDS was determined according to age- and sex-specific reference values reported in the 2004 Flemish growth study. GH status was evaluated in 60 of the 67 patients at the end of treatment by a glucagon stimulation test. The 8 children of peripubertal age received no priming with sex steroids. A peak plasma GH level <10 ng/mL was considered diagnostic for GH deficiency (GHD). Initially, patients with an abnormal response were retested at the onset of puberty. Later in the study, retesting was performed only in those patients who demonstrated a marked decline in growth rate on the height percentile chart.

The onset of puberty was defined as Tanner breast stage 2 in girls and Tanner gonadal stage 2 (testicular enlargement >3 mL and pubic hair stage 2) in boys. Data relating to age at onset of puberty and menarche were available in the medical records of 61 of the 67 patients.

Statistical analyses used height SDS as the dependent variable. Data are expressed as mean ± SD. For the same patients, the paired t test was used to determine whether the ΔSDS for height between 2 evaluation points was significant, with a 2-sided P value ≤.05 considered to indicate statistical significance. Potential influences of sex, age at diagnosis, and intensity of treatment (EORTC protocol 58831 vs protocol 58832 and exposure to cyclophosphamide or cytarabine vs no exposure) on ΔSDS for height and the possible predictive value of the GH stimulation test were explored using univariate and multiple regression techniques. Calculations were performed with SPSS version 19 (IBM, Armonk, New York).

**Results**

Details on sex, age at diagnosis, pubertal status at diagnosis, age at onset of puberty and menarche, availability of data on the GH stimulation test, and the chemotherapeutic treatment are summarized in the Table.

**Longitudinal Growth Analysis**

In Group 1 (n = 45), significant losses in height SDS were observed for the period between the time of diagnosis and the end of treatment (ΔSDS = −0.36; P < .001) (Figure 1). Some limited catch-up growth was seen at 1 year after the end of treatment (ΔSDS = 0.06; P = .96), but again nearly significant losses in height SDS were observed between 1 year after the end of treatment and achievement of FH (ΔSDS = −0.21; P = .056). Mean height SDS decreased...
from 0.76 ± 1.15 at the time of diagnosis to 0.23 ± 0.97 at FH (ΔSDS = −0.53 ± 0.90; P < .001).

In group 2 (n = 22), significant losses in height SDS were observed for the period between the time of diagnosis and the end of treatment (ΔSDS = −0.53; P < .001) (Figure 2). Some growth catch-up was seen at 1 year after the end of treatment (ΔSDS = 0.10; P = .072), but again significant losses in height SDS were observed between 1 year after the end of treatment and achievement of FH (ΔSDS = −0.16; P = .017). Mean height SDS changed from 0.44 ± 1.32 at diagnosis to −0.30 ± 1.13 at FH (ΔSDS = −0.73 ± 0.75; P = .001).

FH Analysis
In the group with FH data (n = 61), mean height SDS decreased from 0.66 ± 1.20 at diagnosis to 0.27 ± 1.11 at the end of treatment (ΔSDS = −0.39 ± 0.48; P < .001) and to 0.07 ± 1.04 at FH (ΔSDS = −0.59 ± 0.86; P < .001). Only 1 patient (from group 2) had an FH below −2 SD.

GH Stimulation Test Results
Four patients had a peak plasma GH level <5 ng/mL (ie, severe GHD), and 13 patients had a peak plasma GH level of 5-10 ng/mL, whereas the majority of patients (n = 43) had a peak plasma GH level >10 ng/mL. The height increase in the year after testing did not differ between the prepubertal patients with a normal response (n = 36) and those with an abnormal (n = 14) response (7.0 ± 1.37 cm vs 6.9 ± 1.34 cm; P = .704). Three patients with a peak plasma GH level <10 ng/mL at the end of treatment were retested at the onset of puberty and demonstrated a normalized response to the GH stimulation test. The other patients with an abnormal response were not retested because they showed no marked decline in growth rate on the height percentile chart.

Pubertal Development
Only 5 of the 67 patients were pubertal at diagnosis, and all 5 progressed to full pubertal maturation. All of the 62 patients who exhibited no clinical signs of pubertal development at diagnosis entered puberty spontaneously. The mean age of the patients with documented menarche was 12.9 years in group 1 and 12.3 in group 2.

Correlation Analysis
The reduction in height SDS from diagnosis to FH was more severe in the male patients than in the female patients (ΔSDS

<table>
<thead>
<tr>
<th>Table. Patient characteristics</th>
<th>Chemotherapy-only group</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>67</td>
<td>45</td>
<td>22</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>40 (60)</td>
<td>27 (60)</td>
<td>13 (59)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>27 (40)</td>
<td>18 (40)</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Age at diagnosis, years, mean (range)</td>
<td>4.5 (0.3-13.7)</td>
<td>4.3 (0.3-13.7)</td>
<td>5.3 (1.3-12.2)</td>
</tr>
<tr>
<td>Age &lt; 4 years at diagnosis, n (%)</td>
<td>29 (43)</td>
<td>21 (47)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Pubertal status at diagnosis, n (%)</td>
<td>Prepubertal 62 (93)</td>
<td>41 (91)</td>
<td>21 (95)</td>
</tr>
<tr>
<td></td>
<td>Pubertal 5 (7)</td>
<td>4 (9)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Age at Tanner stage M2, years, mean (range)</td>
<td>11.0 (9.2-14.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menarche, years, mean (range)</td>
<td>12.6 (10.6-15.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Tanner stage G2, years mean (range)</td>
<td>12.3 (10.6-14.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH stimulation test at the end of therapy</td>
<td>Normal, n (%)</td>
<td>43 (72)</td>
<td>27 (69)</td>
</tr>
<tr>
<td></td>
<td>Abnormal, n (%)</td>
<td>17 (28)</td>
<td>12 (31)</td>
</tr>
<tr>
<td>Treatment; cumulative dose</td>
<td>Prednisolone, mg/m²</td>
<td>1680</td>
<td>1680</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone, mg/m²²</td>
<td>140</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines, mg/m²²</td>
<td>180</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>MTX IV, mg/m²</td>
<td>2000</td>
<td>10 000</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide, g/m² (g)</td>
<td>0 (19) or 2 (23)</td>
<td>3 (22)</td>
</tr>
<tr>
<td></td>
<td>High-dose cytarabine, g/m² (n)</td>
<td>0 (10) or 8 (12)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Changes in mean height SDS at diagnosis; at the end of treatment; at 1 year after treatment; and at achievement of FH for patients in group 1 (n = 45). Vertical bars represent 95% CI for mean. The differences B – A and D – A are statistically significant (both P < .001).
are statistically significant ($P < .001, = .017, and = .001$, respectively).

38 patients, by Vilela and Viana in 42 patients, and by Moëll et al in 42 patients, by Vilela and Viana in 42 patients, and by Holm et al in 42 patients. The reduction in height SDS between diagnosis and the end of treatment noted in the present study is in agreement with those studies, which reported significant declines in both serum insulin-like growth factor 1 and insulin-like growth factor binding protein 3 which were not correlated to a significant decline in height SDS, during maintenance chemotherapy with 6-MP and MTX in 21 children with ALL. Given our findings and those of Marky et al and Smiegelow et al concerning the association between the GH–insulin-like growth factor 1 axis and growth status, we suggest that a direct negative effect of chemotherapy on epiphyseal expansion is likely a more important cause of the growth failure seen during treatment. This suggestion is supported by animal studies showing that doxorubicin causes growth plate thinning in vitro, and that both doxorubicin and MTX cause decreased trabecular volume of the proximal metaphysis of the tibia. Crofton et al reported that the median leg length velocity was lowest at the end of the intensification block of chemotherapy for ALL, and markers of GH status remained within 2 SD of the mean, suggesting that the mechanism of growth impairment at this time was related to the impact of chemotherapy on the growth plate. Catch-up growth never occurs before the completion of chemotherapy. Groot-Loonen et al studied stature growth during maintenance chemotherapy with 6-MP and MTX with or without vincristine and corticosteroids and reported comparable results in both groups, leading to their conclusion that chemotherapy with 6-MP and MTX, not corticosteroids, is the main factor responsible for the suppressed catch-up growth during maintenance chemotherapy for ALL.

In our patients, catch-up growth was seen after the completion of therapy, but regardless, height SDS at 1 year after the completion of treatment remained significantly lower compared with that at diagnosis. This finding is in accordance with the report of Vilela and Viana. In contrast, Moëll et al and Holm et al reported height SDS and z-scores very close to or even higher than the values observed at diagnosis. In the present study, the height increase during the year after the GH stimulation test was not different between the prepubertal patients with a normal GH response and those with an abnormal GH response, implicating either a lack of persistent

$$= -0.85 \pm 0.64 \text{ vs } -0.38 \pm 0.96; P = .036.$$ This difference in reduction in height SDS between the sexes did not occur during chemotherapy, and was seen only after cessation of treatment ($P = .472 \text{ vs } P = .008$).

The $\Delta$SDS for height from the time of diagnosis to the end of treatment or achievement of FH was not correlated with age at diagnosis or age under or over 4 years at diagnosis. No correlation was observed between $\Delta$SDS for body mass index during treatment and pubertal status at diagnosis. Moreover, no correlation was seen between the prevalence of an abnormal GH stimulation test and the intensity of chemotherapy, or between the intensity of treatment or GH stimulation test result and the $\Delta$SDS for height from the time of diagnosis or the end of treatment to the achievement of FH.

### Discussion

Our data demonstrate a modest but significant decrease in FH SDS in adult survivors of childhood ALL treated with multiagent chemotherapy without CRT, irrespective of the age at onset of chemotherapy and GH status at the cessation of treatment. Two-thirds of the height deficit observed from the time of diagnosis until achievement of FH occurred during the treatment. All but 1 patient ultimately achieved adult height within the normal range.

The effect of chemotherapy on linear growth during the treatment of ALL without CRT was studied by Sklar et al in 38 patients, by Vilela and Viana in 42 patients, and by Holm et al in 42 patients. The reduction in height SDS between diagnosis and the end of treatment noted in the present study is in agreement with those studies, which reported height losses ranging from $-0.17 \text{ to } -0.41 \text{ SDS}$. Diminished growth rate with bone age retardation during treatment for ALL is well recognized and attributed mainly to the adverse effects of chemotherapy on growth. The literature contains no detailed studies of GH status in children during chemotherapy for ALL, except a small study reported by Marky et al in which 17 children treated for ALL with 3 different CNS preventive regimens were followed with repeated 24-hour GH profiles obtained over a 24-month period. The 6 children who received only chemotherapy demonstrated no obvious change in GH secretion, except for completely suppressed GH secretion during dexamethasone treatment, which returned to a normal pattern and amount after this treatment.

Given the lack of data, we evaluated GH status at the end of chemotherapy using a standardized pharmacologic stimulation test. The majority (72%) of patients exhibited a normal GH peak after glucagon stimulation. In addition, there was no correlation between the reduction in height SDS during chemotherapy and the response to this test. Smiegelow et al reported significant declines in both serum insulin-like growth factor 1 and insulin-like growth factor binding protein 3 which were not correlated to a significant decline in height SDS, during maintenance chemotherapy with 6-MP and MTX in 21 children with ALL. Given our findings and those of Marky et al and Smiegelow et al concerning the association between the GH–insulin-like growth factor 1 axis and growth status, we suggest that a direct negative effect of chemotherapy on epiphyseal expansion is likely a more important cause of the growth failure seen during treatment. This suggestion is supported by animal studies showing that doxorubicin causes growth plate thinning in vitro, and that both doxorubicin and MTX cause decreased trabecular volume of the proximal metaphysis of the tibia. Crofton et al reported that the median leg length velocity was lowest at the end of the intensification block of chemotherapy for ALL, and markers of GH status remained within 2 SD of the mean, suggesting that the mechanism of growth impairment at this time was related to the impact of chemotherapy on the growth plate. Catch-up growth never occurs before the completion of chemotherapy. Groot-Loonen et al studied stature growth during maintenance chemotherapy with 6-MP and MTX with or without vincristine and corticosteroids and reported comparable results in both groups, leading to their conclusion that chemotherapy with 6-MP and MTX, not corticosteroids, is the main factor responsible for the suppressed catch-up growth during maintenance chemotherapy for ALL.

In our patients, catch-up growth was seen after the completion of therapy, but regardless, height SDS at 1 year after the completion of treatment remained significantly lower compared with that at diagnosis. This finding is in accordance with the report of Vilela and Viana. In contrast, Moëll et al and Holm et al reported height SDS and z-scores very close to or even higher than the values observed at diagnosis. In the present study, the height increase during the year after the GH stimulation test was not different between the prepubertal patients with a normal GH response and those with an abnormal GH response, implicating either a lack of persistent

![Figure 2. Changes in mean height SDS at diagnosis; at the end of treatment; at 1 year after treatment; and at achievement of FH for patients in group 2 (n = 22). Vertical bars represent 95% CI for mean. Differences B – A, D – C, and D – A are statistically significant ($P < .001, = .017, and = .001$, respectively).](image-url)
GHD in those with a low GH reserve or low reliability of pharmacologic testing for GHD.

After the catch-up growth in the first years after the cessation of therapy, we again observed a modest, progressive height decline that did not result in a marked decline in growth rate on the height percentile chart. In clinical practice, we do not recommend testing for GHD except in patients with a declining growth curve, given that GHD requiring GH replacement therapy has reported prevalences of 1.2% and 0.9% of childhood survivors of ALL who were treated with chemotherapy only.

At FH, the patients showed a significant height deficit of 0.59 SDS ($P < .001$) compared with the height SDS at diagnosis. This finding supports the results of Sklar et al and Vilela and Viana and challenges the conclusions of Holm et al, Katz et al, and Bongers et al, who reported no significant changes in FH SDS in patients who underwent treatment for ALL that did not include CRT. The primary explanation for these contradictory findings is the difference in intensity of the chemotherapeutic regimens applied. In contrast to the patients in the present study, almost all patients in the studies of Sklar et al and Vilela and Viana received a chemotherapeutic regimen categorized as standard according to Sklar et al, with a 3-drug induction regimen (eg, L-asparaginase, vincristine, prednisone) and a 4-drug maintenance regimen (eg, MTX, 6-MP, prednisone, vincristine). The patients in our study received a chemotherapeutic regimen categorized as moderate according to the criteria of Sklar et al, with the addition of 1 or more agents (eg, daunorubicin, doxorubicin, cyclophosphamide, cytarabine). It is possible that the exposure to daunorubicin, doxorubicin, and an intermediate or high dose of IV MTX makes the difference, given the similar corticosteroid exposure in the standard-risk and moderate-risk regimens. In the present study, the ΔSDS for height from the time of diagnosis to achievement of FH was not correlated with the intensity of treatment, but all patients received a regimen of at least moderate intensity. The exposure to higher doses of MTX, cyclophosphamide, and cytarabine in some patients did not make a difference. In contrast to patients treated with CRT, in our patients treated only with chemotherapy, the decrease in height SDS was not correlated with age at diagnosis.

An unexpected finding was the greater decrease in height SDS seen in male patients. This difference in the reduction in height SDS between the sexes occurred only after cessation of treatment. Because age at the end of treatment was similar in the male and female patients, a possible explanation for this finding is the longer interval between the end of treatment and the achievement of FH in males.

Childhood ALL is predominantly a disease of young children, with only a minority of patients pubertal at diagnosis. Only 5 of the 67 patients were pubertal at diagnosis, too few to enable evaluation of the influence of pubertal status at diagnosis on the achievement of FH.

In conclusion, chemotherapy of at least moderate intensity as currently used to treat childhood ALL is associated not only with impaired linear growth during treatment, but also with a modest reduction in FH. The suppression of the GH secretion seen at the end of treatment in 28% of patients was not correlated with the reduction in height SDS from diagnosis or end of treatment to FH. In all likelihood, a direct negative effect of chemotherapy on the epiphyses is related to modestly impaired linear growth seen many years after cessation of treatment. The primary explanation for the lack of significant change in height SDS after treatment of ALL without CRT reported in previous studies is the difference in intensity of the chemotherapeutic regimens applied.

We thank Ellen Deschepper (Department of Public Health, Ghent University) for valuable statistical support.

Submitted for publication Aug 24, 2012; last revision received Oct 22, 2012; accepted Dec 12, 2012.
Reprint requests: Els Vandecruys, MD, Department of Pediatric Hemato-Oncology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium.
E-mail: els.vandecruys@ugent.be

References


