Distinct Impact of Imatinib on Growth at Prepubertal and Pubertal Ages of Children with Chronic Myeloid Leukemia

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Objective To determine the extent of growth impairment resulting from imatinib treatment in children with chronic myeloid leukemia (CML).

Study design Clinical records of 48 chronic-phase CML children administered imatinib as the first-line therapy between 2001 and 2006 were analyzed retrospectively. Cumulative change in height was assessed using the height height-SDS and converted height data from age- and sex-adjusted Japanese norms.

Results A decrease in height-SDS was observed in 72.9% of children, with a median maximum reduction in height-SDS of 0.61 during imatinib treatment. Median follow-up time was 34 months (range, 10-88 months). Growth impairment was seen predominantly in children who started imatinib at a prepubertal age compared with those who started at pubertal age. Growth velocity tended to recuperate in prepubertal children with growth impairment, as they reached pubertal age, suggesting that imatinib had little impact on growth during puberty.

Conclusions Growth impairment was a major adverse effect of long-term imatinib treatment in children with CML. We report the distinct inhibitory effect of imatinib on growth in prepubertal and pubertal children with CML. We should be aware of growth deceleration in children, especially in young children given imatinib before puberty and subjected to prolonged exposure. (J Pediatr 2011; __:__ - __).

Since the introduction of imatinib, the treatment of chronic myeloid leukemia (CML) has changed from cure by allogeneic stem cell transplantation to maintenance of the best achievable treatment response (hematologic, cytogenetic, and molecular responses). Various side effects, including nausea, vomiting, diarrhea, skin rash, edema, elevated liver enzyme values, and cytopenia, are known to be common during imatinib treatment, but generally are mild to moderate. However, the long-term side effects of imatinib therapy remain unknown, and its effects on growth are a major concern when treating children. Growth deceleration has been reported in 3 children as well as in a cohort given imatinib. The present study was conducted to evaluate the effect of imatinib on growth in children and adolescents with CML.

Methods

In Japan, imatinib was approved and became available for treatment of CML in December 2001. The Japanese Pediatric Leukemia/Lymphoma Study Group’s CML Committee reviewed records of 99 Japanese children under age 18 years diagnosed with chronic-phase CML between 2001 and 2006. Among these children, 76 who received imatinib as first-line therapy were eligible for the study. Concurrent hydroxyurea administration was permitted. Exclusion criteria were as follows: (1) reached final height at the time of diagnosis (n = 3); (2) afflicted by a chronic disease (eg, schistorrachis) or on any treatment that could affect growth (n = 4); and (3) a follow-up period of <10 months while receiving imatinib (n = 21). Forty-eight children (21 girls, 27 boys) met these criteria and were enrolled in the study. The study design was approved by the Keio University School of Medicine’s Ethics Committee.
Height–Growth Evaluation
As part of the medical examination, height was measured by experienced medical workers at the start of imatinib treatment and at follow-up visits. Height data were converted to numbers with SDs using age- and sex-adjusted Japanese norms to give SDSs. Growth while on imatinib therapy was assessed using cumulative change in height-SDS (ΔSDS) from the start of imatinib treatment to the annual follow-up time points. Minimum height-ΔSDS was determined as the lowest value of annually calculated height-ΔSDS in each patient. Average dose of imatinib \( d_{\text{ave}} \) (mg/m\(^2\)) for an individual during the administration period \( i \) from 1 through \( n \) during \( l \)-year treatment was calculated using the following formulas:

\[
\bar{d} = \frac{\sum_{i=1}^{n} d_{mi} \cdot BSA_{j}}{\sum_{i=1}^{n} m_{i}} \cdot BSA = \sum_{i=1}^{n/l} BSA_{j} \cdot \sum_{i=1}^{n/l} k_{j}, \quad \text{and} \quad d_{\text{ave}} = \frac{\bar{d}}{BSA},
\]

where \( d \) is the dose of imatinib, \( m \) is the number of days of imatinib administration, and \( BSA \) is body surface area (BSA). BSA in the \( j \)th year (BSA\(_j\)) was calculated from data obtained at the observation time point closest to the \( j \)th full-year point within 6 months. The value of \( k_{j} \) is 1 if BSA\(_j\) is available at the \( j \)th year and 0 otherwise. The data after reaching final height were censored for 2 patients. The final height was defined as the maximum height measured when height increase velocity slowed to <1 cm per year. In this study, age threshold equivalent to the onset of puberty was defined as 9 years for girls and 11 years for boys, as generally agreed upon by pediatricians.

Statistical Analyses
Statistical differences in height-SDS between 2 time points—at the commencement of imatinib treatment and at final follow-up—within the cohort were assessed using the Wilcoxon signed-rank test. Statistical differences between the 2 subgroups classified according to minimum height-ΔSDS were assessed using the Mann-Whitney \( U \) test. The statistical differences among the 3 subgroups classified according to the average imatinib dose were evaluated using the Steel-Dwass test. The statistical differences among all annually calculated height-ΔSDS values during imatinib therapy in prepubertal and pubertal children at the commencement of imatinib treatment were assessed using the Tukey-Kramer honestly significant difference test.

Results
The median age at diagnosis was 9 years (range, 2-15 years). The median average imatinib dose was 287 mg/m\(^2\) (range, 161-543 mg/m\(^2\)), and median follow-up was 34 months (range, 10-88 months). The overall median height of the 48 children was nearly normal at the start of imatinib treatment (median height-SDS, 0.01; range, −2.30 to 1.50), but was decreased significantly at the final measurement, with a median height-SDS of −0.85 (range, −2.80 to 1.30) \( (P < .001, \text{Wilcoxon signed-rank test}) \), indicating that imatinib adversely affected growth (Figure 1, A and B). Height <−2 SD at the last follow-up was observed in 6 children (12.5%), excluding 1 child whose height was <−2 SD at the start of imatinib treatment. A decrease in height-SDS of >0.5 SD was observed in 25 children (52.1%), including 16 (33.3%) with a decrease of >1 SD during imatinib treatment. The median minimum annually calculated height-ΔSDS during follow-up was −0.61 (range, −2.20 to 0.60) (Figure 1, C).

We next divided the study cohort according to their minimum height-ΔSDS into 2 subgroups: <−0.5 \( (n = 25) \) and ≥−0.5 \( (n = 23) \). Sex distribution, average imatinib dose, and proportion of patients with hydroxyurea administration were comparable between the 2 subgroups (Table). The greatest significant difference observed between the 2 subgroups was age at initiation of imatinib treatment. The proportion of prepubertal children was significantly higher in the minimum height-ΔSDS <−0.5 subgroup than in the ≥−0.5 subgroup. In contrast, the ≥−0.5 subgroup consisted mainly of children at pubertal age at the start of imatinib treatment.

To evaluate the relationship between administered imatinib dose and growth impairment, we divided the cohort according to the average administered dose for each individual and

![Figure 1](image)

**Figure 1.** Change in height-SDS during imatinib treatment. Height-SDS is shown at A, the commencement of imatinib treatment and B, at the last follow-up. C, Minimum height-ΔSDS during imatinib treatment. The median value is indicated above each plot. \( n \), number of patients.
recommended pediatric doses for treating chronic-phase CML (260-340 mg/m²)⁶ into 3 subgroups: <260 mg/m² (n = 17), 260-340 mg/m² (n = 19), and >340 mg/m² (n = 12). The median minimum height-ΔSDS of these 3 subgroups was -0.6 (median dose, 222 mg/m²), -0.48 (median dose, 293 mg/m²), and -0.85 (median dose, 360 mg/m²), respectively, indicating no significant difference among the 3 subgroups.

Representative growth charts of children at various ages at the start of imatinib treatment are shown in Figure 2. Growth impairment was particularly significant in children who were prepubertal at the start of imatinib treatment (Figure 2, A and B), and only mild growth impairment or no impairment was seen in most of the children who were pubertal at the start of imatinib treatment (Figure 2, C and D). However, the prepubertal children with growth impairment regained growth velocity as they reached pubertal age (Figure 2, E-H).

Mariani et al² reported a 9-year-old boy who demonstrated impaired growth shortly after the start of imatinib treatment but experienced catch-up growth with the onset of puberty. Thus, to evaluate whether children at pubertal age evade growth deceleration, we dichotomized the study cohort into 2 subgroups: children who started imatinib at prepubertal age (n = 27) and those who did so at pubertal age (n = 21). In the former group, height-ΔSDS began to decline during the first year of imatinib treatment, resulting in significant deceleration in growth. In the latter group, height-ΔSDS remained steady through imatinib treatment, suggesting that imatinib has little effect on growth in pubertal children (Figure 3).

Collectively, our data show a high frequency of growth impairment and >0.5 SD of cumulative decrease in height-SDS in children given imatinib for chronic-phase CML. This growth impairment was seen predominantly in young children who were started imatinib at prepubertal age.

### Discussion

Imatinib is now a major option as the first-line therapy for childhood CML.⁶-⁹ Thus, it is important for clinicians to be aware of its possible long-term effects. Imatinib inhibits several tyrosine kinases, including c-abl, c-kit, c-fms, and platelet-derived growth factor (PDGF) receptors.⁷,¹⁰,¹¹ Several studies in adults have suggested that inhibition of c-kit, c-fms, and PDGF receptors results in modulation of bone metabolism.¹²-¹⁵ Inhibition of osteoclasts and osteoblasts may result in dysregulated bone remodeling.¹¹,¹⁵-¹⁷ Three recently published case reports indicated growth impairment as an adverse effect of long-term imatinib treatment in children.²-⁴ In addition, a French group reported a significant decrease in height-SDS in 22 children, with a median difference of -0.37 (range, -1.09 to 0.14; P < .0001) during the first year of imatinib treatment.² Although the impact of imatinib on growth was noticeable in children in these previous studies, it has not yet been fully elucidated.

In our study of 48 children with chronic-phase CML, the severity of growth impairment was related to age at the start of imatinib treatment. Growth impairment was observed predominantly in children at prepubertal age compared with children at pubertal age. In children who started imatinib at prepubertal age, height-ΔSDS decreased during treatment, and in most cases, more than 2 years of continuous treatment was necessary to exhibit a reduction in height-SDS of >0.5 SD (Figure 3). Although 4 children who started imatinib at prepubertal age were included in the height-ΔSDS ≥-0.5 subgroup, these children were receiving imatinib for <2 years (Table), possibly indicating a high risk for developing severe growth impairment thereafter. We compared the distinct impact of long-term imatinib treatment on growth in prepubertal and pubertal children with CML.

Because the average imatinib dose varied among patients in our cohort, analysis was also performed according to the administered dose of imatinib. Although not significant, children exposed to imatinib doses >340 mg/m² showed a greater decrease in height-SDS compared with those exposed to lower doses, suggesting the need for further analysis to determine the correlation between imatinib dose and severity of growth impairment.

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**Table. Patient characteristics**

<table>
<thead>
<tr>
<th>Minimum height-ΔSDS</th>
<th>&lt; -0.5 (n = 25)</th>
<th>≥ -0.5 (n = 23)</th>
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<tr>
<td>Age at the commence-</td>
<td></td>
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<tr>
<td>ment of imatinib</td>
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<tr>
<td>Median, years</td>
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<td>12</td>
<td>&lt;.001</td>
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<tr>
<td>Range, years</td>
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<tr>
<td>Prepubertal age, n (%)</td>
<td>23 (92.0)</td>
<td>4 (17.4)</td>
<td>&lt;.001</td>
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<tr>
<td>Pubertal age, n (%)</td>
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<td>19 (82.6)</td>
<td>&lt;.001</td>
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<td>Male sex, n (%)</td>
<td>14 (56.0)</td>
<td>13 (66.5)</td>
<td>.9808</td>
</tr>
<tr>
<td>Duration of imatinib treatment, months, median (range)</td>
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<td></td>
<td></td>
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<tr>
<td>Prepubertal age</td>
<td>42 (19-88)</td>
<td>14 (10-22)</td>
<td>.009</td>
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<tr>
<td>Pubertal age</td>
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<td>26 (10-61)</td>
<td>.406</td>
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<tr>
<td>Average imatinib dose, mg/m²</td>
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<td>.272</td>
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<tr>
<td>Range</td>
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<td>197-376</td>
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<td>Hydroxyurea adminis-</td>
<td>2 (8.0)</td>
<td>3 (13.0)</td>
<td>.577</td>
</tr>
</tbody>
</table>

**Footnotes:**

*Prepubertal age: males, <11 years; females, <9 years.
†Pubertal age: males, ≥11 years; females, ≥9 years.
Figure 2. A and B, Representative height growth chart at the start of imatinib treatment of prepubertal children, and C and D, pubertal children. Growth impairment was observed in children at prepubertal age, but imatinib had little affect on growth in children at pubertal age. Impaired growth before puberty recovered as children reached pubertal age even during imatinib treatment. Catch-up growth was observed at E and F, approximately 11 years for girls, and G and H, 13 years for boys.
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We thank all of the participating institutions in Japanese Pediatric Leukemia/Lymphoma Study Group and all members of the Chronic Myeloid Leukemia Committee for their contributions to exact follow-up and data collection in each case.

References


