Effect of the tyrosine kinase inhibitors on the growth in children with Philadelphia chromosome–positive acute lymphoblastic leukemia: a case–control study

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Summary

Background First-generation ABL-targeted tyrosine kinase inhibitor (TKI) imatinib is known to retard growth in children but it is not known if the second-generation ABL-targeted TKI dasatinib has the same effect. We aimed to determine the impact of the first- or second-generation TKI on the growth of children treated for Philadelphia chromosome-positive (Ph^+) childhood acute lymphoblastic leukemia (ALL).

Methods We evaluated the longitudinal growth changes in 140 children with Ph^+ ALL treated with imatinib or dasatinib in additional to intensive cytotoxic chemotherapy and 280 matched controls treated with the same intensity of cytotoxic chemotherapy without TKI on Chinese Children's Cancer Group ALL-2015 protocol between 2015 and 2019. We retrospectively reviewed the height data obtained during routine clinic visits at 4 time points: at diagnosis, the end of therapy, 1 year and 2 years off therapy. Height z Scores were derived with the aid of WHO Anthro version 3.2.2 and WHO AnthroPlus version 1.0.4, global growth monitoring tool.

Findings This study consisted only patients who have completed all treatment in continuous complete remission without major events, including 33 patients randomized to receive imatinib, 43 randomized to receive dasatinib, and

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64 assigned to receive dasatinib. Similar degree of loss of height z scores from diagnosis to the end of therapy was observed for the 33 imatinib- and the 107 dasatinib-treated patients (median △ = –0.84 vs. –0.88, P = 0.41). Adjusting for height z score at diagnosis, puberty status, and sex, there was no significant difference in the longitudinal mean height z scores between patients treated with imatinib and those with dasatinib (0.08, 95% CI, –0.22 to 0.38, P = 0.60). The degree of loss of height z scores from diagnosis to end of therapy was significantly greater in the 140 TKI-treated patients than the 280 controls (median △ = –0.88 vs. –0.18, P < 0.001). The longitudinal mean height z scores in the TKI-treated patients were significantly lower than those of the controls (–0.84, 95% CI, –0.98 to –0.69; P < 0.001).

Interpretation These data suggest that dasatinib and imatinib have the similar adverse impact on the growth of children with Ph^+ ALL.

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Keywords: Tyrosine kinase inhibitor; Dasatinib; Imatinib; Philadelphia chromosome-positive leukemia; Acute lymphoblastic leukemia; Height; Growth; Puberty

Research in context

Evidence before this study

It is well recognized that intensive conventional cytotoxic chemotherapy resulted in growth retardation in children with ALL. However, little is known about the impact of the first- or second-generation ABL-targeted TKI on the growth of children treated for Ph^+ ALL. We searched PubMed for reports published in English up to February 1, 2023, using the terms "tyrosine kinase inhibitors," "growth," "height," "pediatric leukemia," and "Philadelphia chromosome" in various combinations. Most published papers confirmed the first-generation imatinib caused growth retardation in children treated for Ph^+ chronic myeloid leukemia (CML). One retrospective study showed that dasatinib, a second-generation TKI, caused a slight decrease in height z score in pre-pubertal and pubertal children treated for CML. Data on the impact of imatinib or dasatinib on the growth in children treated for Ph^+ ALL were limited to only two small studies. However, the results of both studies are inconclusive because of small sample sizes, heterogeneity in treatment regimens, and short follow-up.

Added value of this study

This study showed that there was no significant difference in the longitudinal height z scores during and after therapy and in the degree of height z score loss from diagnosis to the end of therapy between imatinib-treated or dasatinib-treated patients. There was significant difference in the longitudinal mean height z scores between either TKI-treated patients and the controls who received the same intensity of cytotoxic chemotherapy without TKI, and the amount of loss of height z scores from diagnosis to the end of therapy was significantly greater in the TKI-treated patients than controls.

Implications of all the available evidence

These data showed that dasatinib and imatinib have the similar adverse impact on the growth of children with Ph^+ ALL. Our results suggest that dasatinib is preferable than imatinib to treat Ph^+ ALL because it yields superior event-free survival in a previous randomized trial without causing additional adverse toxicity including growth retardation as demonstrated in this study.

Introduction

With improved risk-directed treatment and supportive care, the 5-year overall survival rate for pediatric patients with acute lymphoblastic leukemia (ALL) has increased to approximately 90%.[1–4] Recent research has been focused on the use of targeted therapy to further improve the survival rates while decreasing toxicities. Contemporary treatments for Philadelphia chromosome-positive (Ph^+) ALL with *BCR::ABL1* fusion comprise intensive chemotherapy and a ABL-targeted tyrosine kinase inhibitor (TKI).[1,2] It is well recognized that intensive conventional cytotoxic chemotherapy resulted in growth retardation and loss of final adult height in children with ALL.[5–7] However, little is known about the impact of the first- or second-generation ABL-targeted TKI on the growth of children treated for Ph^+ ALL.

Imatinib and dasatinib are the most frequently used ABL-targeted TKIs against Ph^+ (*BCR::ABL1*$^+$) leukemia. As a single agent, the first-generation TKI imatinib caused growth retardation in pre-pubertal and pubertal children treated for Ph^+ chronic myeloid leukemia (CML).[8–14] One retrospective study showed that dasatinib, a second-generation TKI, caused a slight decrease in height z score in pre-pubertal and pubertal children treated for CML.[15] Data on the impact of TKI on the growth in children treated for Ph^+ ALL were limited to only two small studies.[12,16] In the first study, 19 children aged 9.0 ± 4.6 years were treated with cytotoxic chemotherapy and one or more TKIs including imatinib, dasatinib, nilotinib or ponatinib, and in 63.2% of them also cranial irradiation or total body irradiation.[12] All patients experienced a decrease in height z score from a median of –0.03 at diagnosis to –0.79 at the last follow-up at 3.3 ± 1.6 years but there were negligible changes in the scores from the cessation of TKI treatment to one year post in the eight patients who stopped treatment.[12] In the second study, the investigators follow the growth of 298 children with non-Ph^+ ALL treated with conventional chemotherapy, 39 with Ph^+ ALL treated with conventional chemotherapy and imatinib, and 7 with Ph^+ ALL treated with conventional chemotherapy and dasatinib.[16] The 39 imatinib-treated patients had significantly decreased height z scores from diagnosis (0.58 ± 1.04) to 2 years after the treatment (–0.47 ± 0.97, $P < 0.001$) but surprisingly there was no significant reduction in the height z scores among patients treated with only conventional chemotherapy nor those with conventional chemotherapy and dasatinib.[16] For 10 children who were initially treated with imatinib and subsequently changed to dasatinib treatment, there was no significant difference in height z scores at the time of converting to and during dasatinib treatment. The authors postulated that dasatinib may have little adverse effect on growth in children with Ph^+ ALL. However, the results of both studies are inconclusive because of small sample sizes, heterogeneity in treatment regimens, and short follow-up.

We have recently completed the first stratified and randomized clinical trial comparing the efficacy and safety of imatinib and dasatinib treatment in children with Ph^+ ALL who received the same backbone chemotherapy.[17] None of the patients received cranial irradiation nor allogeneic hematopoietic cell transplantation, both of which could adversely affected the growth. This study showed that dasatinib treatment resulted in significantly better event-free survival than imatinib treatment and there were no significant differences in the frequency of severe toxicity between the two treatment groups.[17] This randomized trial provided a unique opportunity to evaluate the potential impact of imatinib and dasatinib on the growth of children treated for Ph^+ ALL.

Methods

Study design and participants

Patients 0–18 years old with a confirmed diagnosis of ALL were enrolled consecutively in the CCCG-ALL-2015 protocol between January 1, 2015 and December 31, 2019 at 20 medical centers in China.[18,19] The study was approved by the ethics committee of each participating institution. Written informed consent was obtained from the parents, guardians, or patients, as appropriate. All patients received risk-stratified and minimal residual disease (MRD)-directed therapy without prophylactic cranial irradiation, modified from the St Jude Children's Research Hospital Total XV and XVI studies[20,21] and the Shanghai Children's Medical Center ALL-2005 trial.[22,23] All patients with Ph^+ ALL enrolled in the study were assigned to the intermediate-risk group to receive intensive cytotoxic chemotherapy. They were stratified by age (<1, 1–9, and ≥10 years) and participating institutions and randomized (1:1) to receive dasatinib (80 mg/m^2 per day, maximal 180 mg per day) (Ph-D group) or imatinib mesylate (300 mg/m^2 per day, maximal 600 mg per day) (Ph-I group) which was started during remission induction therapy and continued to the end of all therapy.[17] Among the first 189 randomized patients, 95 received imatinib, and 94 dasatinib. In October 2018, the interim analysis showed significantly improved 3-year event-free survival in patients treated with dasatinib as compared to those with imatinib. The data and safety monitoring committee recommended to stop the randomization and replace imatinib with dasatinib in all patients who were still receiving treatment and to treat all 103 subsequent newly diagnosed Ph^+ ALL patients with dasatinib. The inclusion criteria for this study consisted of completion of all treatment and continuous complete remission, and exclusion criteria included relapse, abandoned treatment, having received hematopoietic cell transplantation, and lack of data. Based on the criteria, this study included 33 patients in Ph-I group, 43 in Ph-D group and 64 non-randomized group treated with dasatinib.

Patients with Ph-negative ALL who were treated with the same intensity of conventional chemotherapy in the intermediate-risk group as those with Ph^+ ALL in the same protocol and remained in continuous complete remission at three participating hospitals of the study group (Shanghai Children's Medical Center, Children's Hospital of Soochow University, and Institute of Hematology & Blood Diseases Hospital) served as the control group. Patients in the control group were randomized (1:1) to either receive or not to receive seven pulses of vincristine plus dexamethasone given over 8 weeks during the second year of maintenance therapy.[19] Each patient with Ph^+ ALL were matched with two controls by age, sex, and immunophenotype. R program was used to select matched samples of the Ph^+ ALL and control groups with similar covariate distributions. For

age, we categorized age as 0–1, 1–2, 2–3 ..., and created new age variable and used it for exact matching. The only Ph^+ patient underwent allogeneic hematopoietic cell transplantation in the imatinib group was excluded in the analysis.

We retrospectively reviewed the height data obtained during routine clinic visits at 4 time points: at diagnosis, the end of therapy, 1 year and 2 years off therapy (±90 days) for Ph^+ patients and the controls. Patients were excluded from the analyses at a time point and beyond if they had induction failure, relapse in any site, death due to any cause, withdrawal from protocol therapy, transfer to other hospitals, or lost to follow-up. Height z Scores were derived with the aid of WHO Anthro version 3.2.2 and WHO AnthroPlus version 1.0.4, global growth monitoring tool. Pre-pubertal group included girls ≤9 years of age and boys ≤11 years, and those older were considered post-pubertal. Age at diagnosis of ALL was used to categorize individual patient with regard to puberty.

Statistical analysis

Fisher's exact test was used to post hoc analyze clinical characteristics among Ph-D group, non-randomized group and imatinib group, and between patients treated with TKI and those in the control group. The differences in height z score (the Δs) between pairs time points among dasatinib-treated patients, imatinib-treated patients, and the control groups were compared using the Wilcoxon rank sum test. Longitudinal/mixed effect model was used to compare and estimate the difference in longitudinal mean height z scores at the end of therapy, 1 year and 2 years after therapy, with the AR (1) working covariance structure to account for intra-patient (longitudinal) correlation, adjusting for a few covariates as appropriate. Comparison of TKI vs. non-TKI group included baseline height z score at diagnosis, puberty status, and sex as covariates. Similar longitudinal models were applied in the subset analyses within the TKI and control group respectively, or within certain subsets defined by puberty status and sex. All reported P values were 2-sided and were not adjusted for multiple comparisons, with $P < 0.05$ indicating significance. Of the 140 TKI-treated patients, 25 (17.9%) continued to receive TKI beyond the end of continuation treatment based on the parental request. These 25 patients were censored at the time of cessation of continuation treatment. Data reported herein were updated on September 30, 2022. All statistical analyses were conducted with R statistical software, version 4.1.3. (R Project for Statistical Computing [https://www.r-project.org/]).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, patient recruitment, any aspect pertinent to the study, writing of the manuscript or decision to submit it for publication. The corresponding author did not receive payment from a pharmaceutical company or any agency to write this article. The authors were not precluded from accessing data in the study and accept responsibility to submit the manuscript for publication.

Results

Of the 140 children with Ph^+ ALL included in this study, 33 children were randomized to receive imatinib (Ph-I group), 43 randomized to dasatinib (Ph-D group), and 64 assigned to dasatinib (see Methods, Fig. 1). We identified 280 children with Ph-negative ALL serving as matched controls, i.e., receiving the same cytotoxic chemotherapy as Ph+ ALL patients but without TKI treatment. The median follow-up durations were 4.3 years (IQR, 3.4–5.6 years; range, 2.8–7.6 years) for the TKI treated patients, and 5.1 years (IQR, 4.2–6.0 years; range, 3.3–7.6 years) for the controls. The median durations of TKI treatment were 2.9 years (range, 2.4–6.5 years) for all 140 children, 2.8 years (range, 2.4–6.5 years) for Ph-I group, 2.9 years (range, 2.5–6.2 years) for Ph-D group, and 3.0 years (range, 2.5–3.9 years) for non-randomized patients treated with dasatinib. The median age at diagnosis was 7.4 years (range, 1.2–15.9 years) in Ph^+ ALL group and 6.7 years (range, 1.1–16.3 years) in the control group. Clinical characteristics did not differ significantly among Ph-D group, non-randomized group and imatinib group, and between patients treated with either TKI and the control group (Table 1).

Pattern of growth during and after therapy between imatinib- and dasatinib-treated patients

Among dasatinib-treated patients, the median height z core was 0.12 at diagnosis, –0.69 at the end of therapy, –0.51 at 1-year off therapy, and –0.35 at 2-years off therapy (Fig. 2A). Among imatinib-treated patients, the median height z score was –0.25 at diagnosis, –1.01 at the end of therapy, –1.12 at 1 year off therapy, and –0.78 at 2-years off therapy.

We compared the decrease of height z score during therapy (i.e., from diagnosis to the end of therapy) between imatinib-treated and dasatinib-treated patients. Similar degree of height loss was observed for imatinib- and dasatinib-treated patients (median $\triangle$ = –0.84 vs. –0.88, P = 0.41, Fig. 2B). Further, adjusting for height z score at diagnosis, puberty status, and sex, there was no significant difference in the longitudinal mean height z scores across three time points (end of therapy, 1 year and 2 years off therapy) between the two groups: 0.08 (95% CI, –0.22 to 0.38, P = 0.60). We therefore combined imatinib- and dasatinib-treated patients for subsequent analyses. Among the 140 TKI-treated patients, the median height z score decreased from 0.06 at the time of diagnosis to –0.79 at the end of therapy and improved to –0.73 at 1-year off therapy and –0.45 at 2-year off therapy (Fig. 3A).

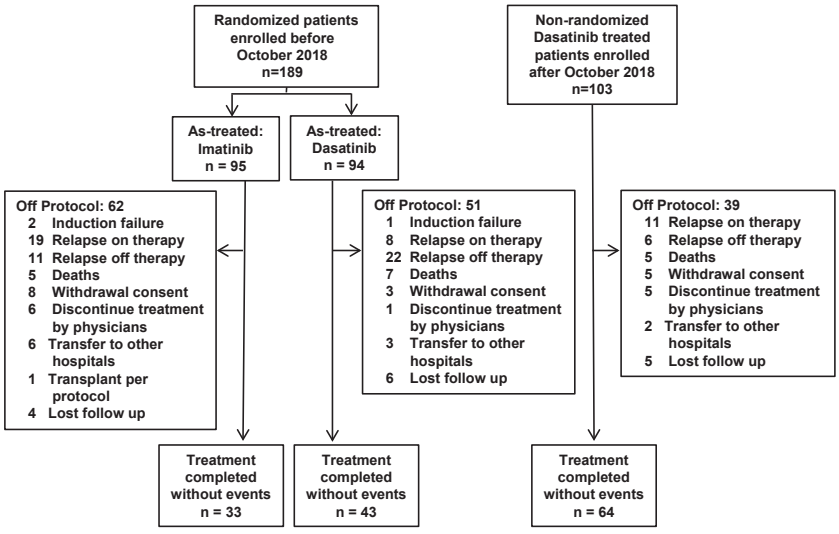

Fig. 1: Flow chat of patient disposition.

Pattern of growth during and after therapy between control group and TKI group

Within the control group, there was no significant difference in the longitudinal mean height z scores between patients randomized to receive treatment with or without the additional vincristine plus dexamethasone pulses (0.02, 95% CI, –0.08 to 0.11; P = 0.74), and therefore they were combined for analyses. Among all 280 controls, the median height z score was 0.34 at the time of diagnosis, decreased to 0.17 at the end of therapy, and then improved to 0.55 at 1 year off therapy and 0.45 at 2 years off therapy (Fig. 3A).

The decrease of median height z scores from diagnosis to the end of therapy was significantly greater in the TKI-treated patients than the controls (median △ = –0.88 vs. –0.18, P < 0.001; Fig. 3B). Further, adjusting for height z score at diagnosis, puberty status, and sex, there was significant difference in the longitudinal mean height z cores between TKI-treated patients and the controls (Fig. 3A). Across all three time points (i.e., at the end of therapy, 1 year and 2 years off therapy), TKI-treated patients had significantly lower mean z score (–0.84, 95% CI, –0.98 to –0.69; P < 0.001) (Fig. 4). The controls recovered more height z scores than the TKI-treated patients between end of therapy and 1-year off therapy (median △ = 0.20 vs. 0.03, P = 0.002) (Table 2). The recovery of height z scores from the end of therapy to 2-year off therapy were not significantly different between the TKI group and the control group, probably due to small number of TKI-treated patients at 2-year off therapy (Table 2).

Clinical Characteristics	Dasatinib group			Ph-I group No. (%)	P value[a]	Total TKI group No. (%)	Control group No. (%)	P value[b]
	Ph-D group No. (%)	Non-randomized No. (%)	P value					
Age at diagnosis, years			0.54		0.53			0.91
1–10	27 (62.8)	44 (68.7)		24 (72.7)		95 (67.9)	192 (68.6)	
≥10	16 (37.2)	20 (31.3)		9 (27.3)		45 (32.1)	88 (31.4)	
Sex			0.20		0.99			0.43
Female	9 (20.9)	21 (32.8)		9 (27.3)		39 (27.9)	89 (31.8)	
Male	34 (79.1)	43 (67.2)		24 (72.7)		101 (72.1)	191 (68.2)	
Immunophenotype			0.99		0.42			0.72
B cell	43 (100)	63 (98.4)		32 (97.0)		138 (98.6)	273 (97.5)	
T cell	0 (0)	1 (1.6)		1 (3.0)		2 (1.4)	7 (2.5)	
Median duration of TKIs treatment (years)	2.9 (2.5–6.2)	3.0 (2.5–3.9)		2.8 (2.4–6.5)		2.9 (2.4–6.5)	/	
Median follow-up time (years)	5.6 (4.1–7.6)	3.4 (2.8–4.0)		5.4 (4.2–7.2)		4.3 (2.8–7.6)	5.1 (3.3–7.6)	

TKI, tyrosine kinase inhibitor. [a]Comparisons between Dasatinib group and Ph-I group. [b]Comparisons between total TKI group and control group.

Table 1: **Patient characteristics.**

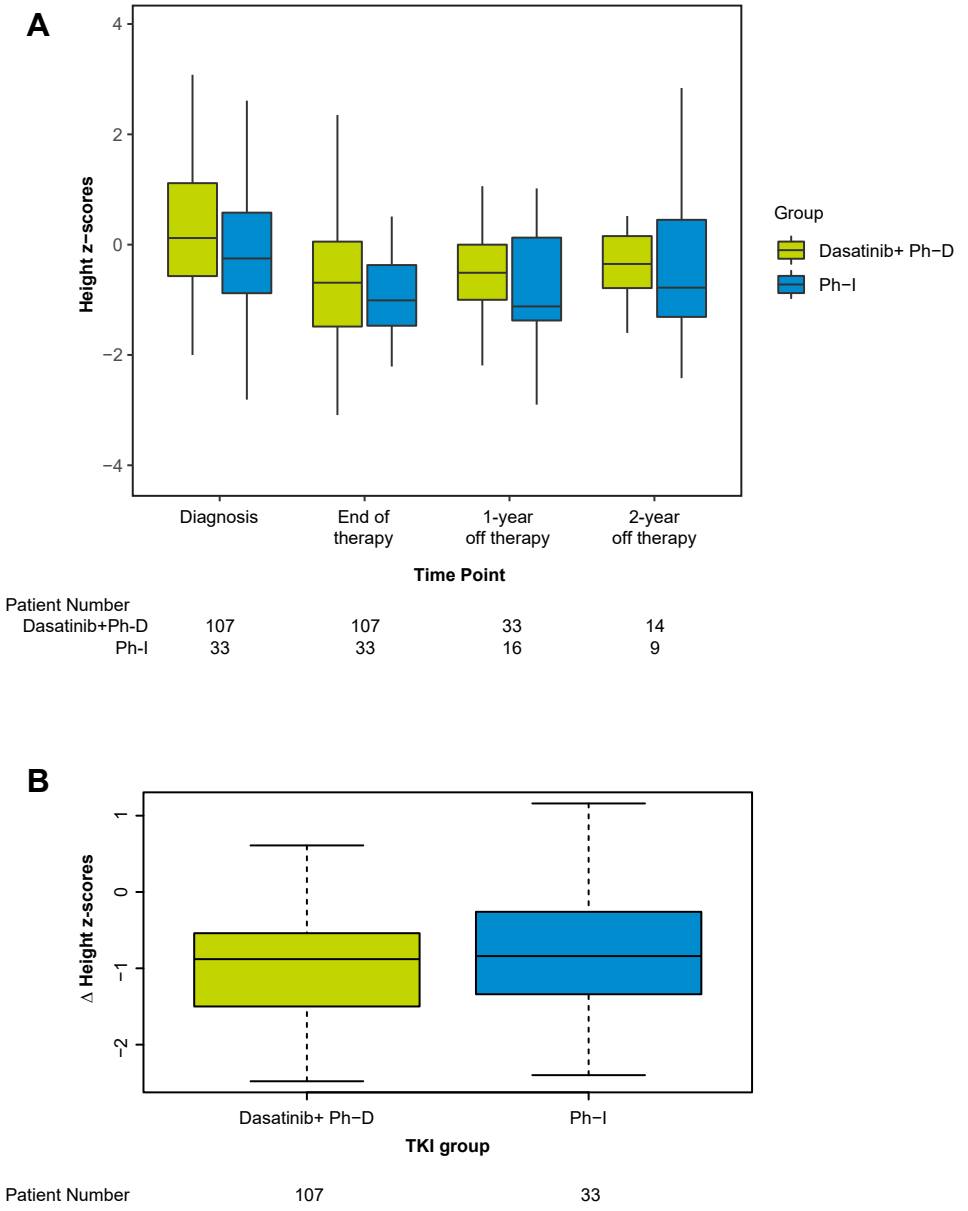

Fig. 2: Longitudinal pattern of height z score in dasatinib-treated (Dasatinib + Ph-D) and imatinib-treated (Ph-I) patients by box plots (A); decrease in height z score during therapy between dasatinib-treated and imatinib-treated patients (B). △Height z scores indicates height z scores at the end of therapy minus height z scores at diagnosis.

Association of clinical characteristics with the pattern of height change in the TKI group and the control group

Among the TKI-treated patients, the height loss from diagnosis to the end of therapy was not significantly different between boys and girls (P = 0.98) nor between pre-pubertal and post-pubertal patients (P = 0.89, Table 3). However, the height z scores decreased during therapy more significantly in post-pubertal boys than in post-pubertal girls (median △ = −1.07 vs. −0.76, P = 0.02, Table 3).

Among the controls, across three time points (i.e., at the end of therapy, 1 year and 2 years off therapy), the longitudinal mean height z score was significantly lower in the post-pubertal patients compared to pre-pubertal patients (−0.63, 95% CI, −0.81 to −0.46; P < 0.001) (Supplemental Fig. S1). There was no significant difference between boys and girls (P = 0.77, data not shown).

Compared to the controls, the TKI-treated patients showed significantly lower longitudinal mean height z scores in various patient subsets: pre-pubertal patients

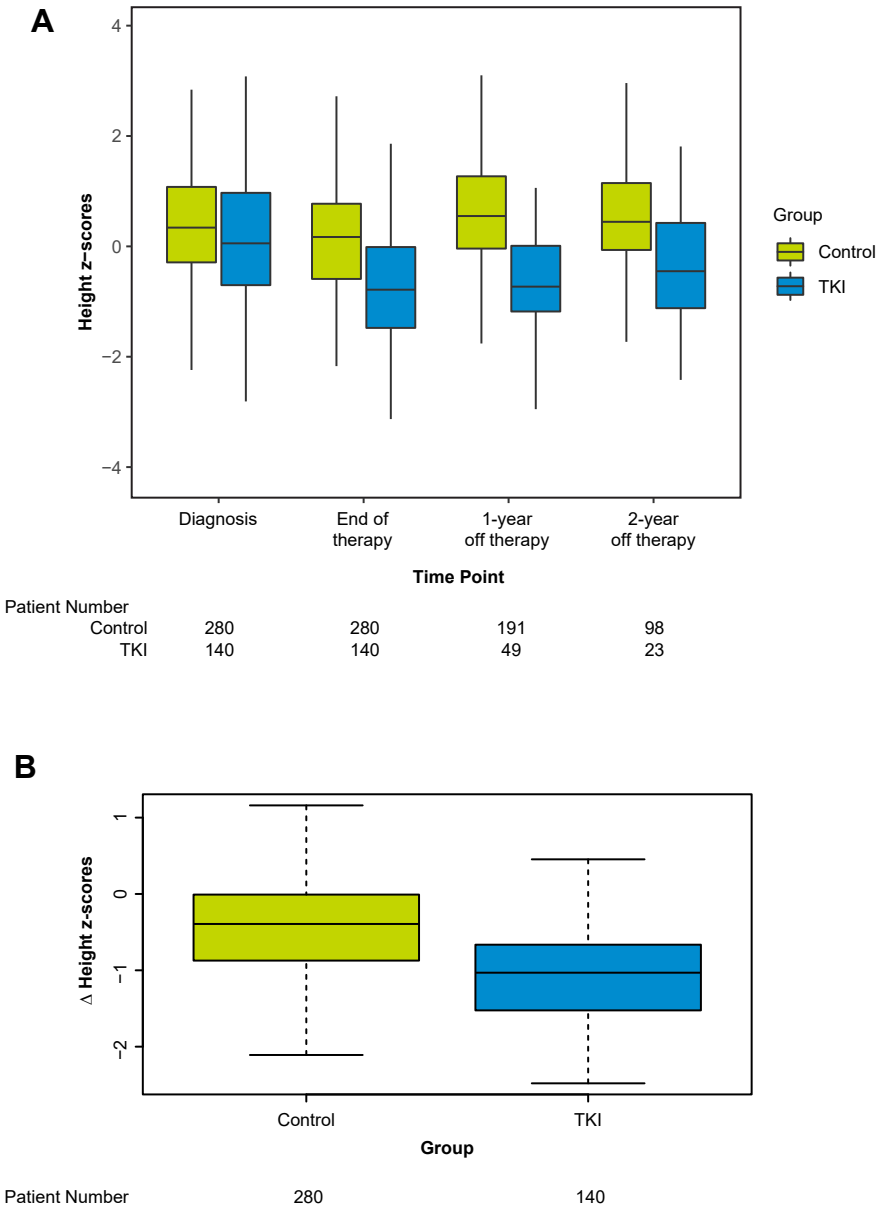

Fig. 3: Longitudinal pattern of height z score for tyrosine kinase inhibitor (TKI)-treated patients and the control group by box plots (A); and height loss during therapy between tyrosine kinase inhibitor treated patients and control group (B). △Height z scores indicates height z scores at the end of therapy minus height z scores at diagnosis.

(–0.97, 95% CI: –1.15 to –0.79; P < 0.001), post-pubertal patients (–0.50, 95% CI: –0.71 to –0.30, P < 0.001), boys (–0.86, 95% CI: –1.04 to –0.68, P < 0.001), and girls (–0.79, 95% CI: –1.06 to –0.52; P < 0.001) (Supplemental Fig. S2A–S2D, respectively).

Discussion

This study showed that there was no significant difference in the longitudinal height z scores during and after therapy and in the degree of height z score loss from diagnosis to the end of therapy between imatinib-treated or dasatinib-treated patients. These findings showed that imatinib and dasatinb administered at the prescribed dosages (300 mg/m^2 and 80 mg/m^2 per day, respectively) have similar growth inhibitory effect. There was significant difference in the longitudinal mean height z scores between TKI-treated patients and the controls, and the amount of loss of height z scores from diagnosis to the end of therapy was significantly greater in the TKI-treated patients than controls.

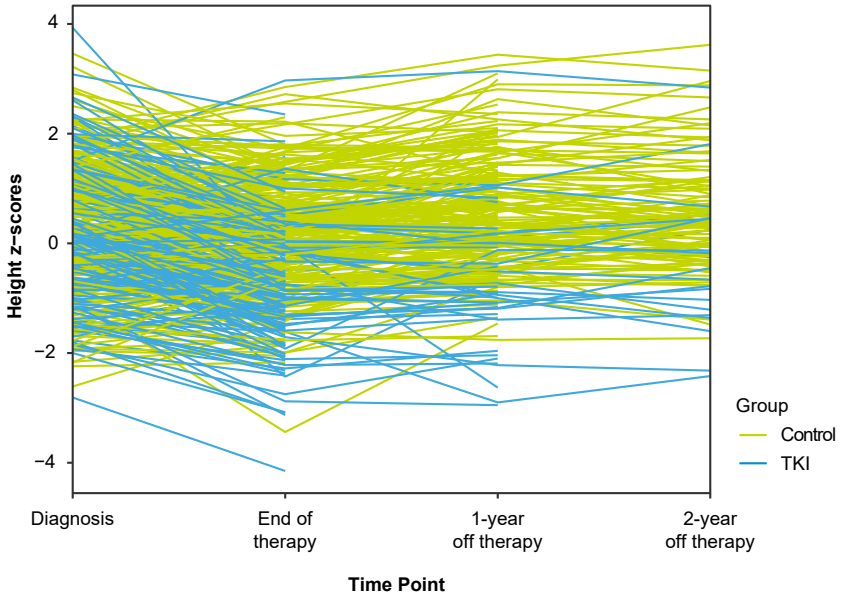

Fig. 4: Longitudinal changes in height z scores by time timepoints for individual patients treated with tyrosine kinase inhibitor (TKI) and for individual control patients. The green lines show data for the control patients and the blue lines for TKI-treated patients.

In this first randomized study comparing imatinib and dasatinib treatment,[17] we administered dasatinib at a dosage of 80 mg/m^2 per day which is equivalent to that (140 mg per day) typically used in adult patients with Ph$^+$ ALL[24,25] and higher than that (60 mg/m^2 per day) commonly used in pediatric patients.[26,27] Our dasatinib-treated patients had significantly better event-free survival and CNS control than imatinib-treated patients.[17] In fact, only 1 of our 92 dasatinib-treated patients developed isolated CNS relapse despite none of them received cranial irradiation or bone marrow transplant.[17] By contrast, 4 of 60 and 4 of 106 patients in the two pediatric trials using lower dose of dasatinib at 60 mg/m^2 per day developed isolated CNS relapse, despite 38% and 19% of their patients, respectively, received cranial irradiation or transplantation.[26,27] In this regard, a recent study showed that the dosage of dasatinib that we used enhanced the penetration of the drug into the cerebrospinal fluid than the lower dosage.[28] The dasatinib-treated patients did not have excessive toxicity as compared to those treated with imatinib in our trial.[17]

Time point 1	Time point 2	△Height Z scores[a] median (range): TKI	△Height Z scores[a] median (range): control	P value
Diagnosis	End of therapy	−0.88 (−4.25, 1.47)	−0.18 (−2.44, 1.84)	**<0.001**
End of therapy	1 year off therapy	0.03 (−2.59, 1.81)	0.20 (−1.02, 3.30)	**0.002**
End of therapy	2 years off therapy	−0.01 (−1.51, 1.79)	0.22 (−1.37, 1.66)	0.20

Note: P values less than 0.05 showed in bold. TKI, tyrosine kinase inhibitor. [a]△Height z scores indicate height z scores at Time point 2 minus that at Time point 1.

Table 2: **△Height z scores comparisons between two time points in tyrosine kinase inhibitor treated patients and control group.**

Here we showed that our dasatinib-treated patients also did not have more decrease in height z scores than imatinib-treated patients. Thus, our results suggest that dasatinib is preferable than imatinib in the treatment of childhood Ph$^+$ ALL.

There was no significantly difference in grade 4 adverse events including infections between Ph$^+$ ALL patients and the control group (18/140 vs. 25/280, P = 0.23). The findings of significant growth deceleration during treatment in our patients treated for Ph$^+$ ALL are consistent with the additive growth inhibitory effects of ABL TKI to intensive cytotoxic chemotherapy. It has been shown that growth stunting effect of TKI was more prominent in patients treated for CML at the pre-pubertal age than those at the pubertal age 8[8,10,13–15]; perhaps rapid pubertal growth acceleration could render patients more resistant to growth inhibitory effects of TKI. TKIs have off-target endocrinological consequences affecting the growth rate and bone metabolism in children.[29–33] The underlying mechanisms of TKI on growth deceleration have variously been attributed to alterations in bone mineral and vitamin D metabolism and disruption of the growth hormone-insulin-like growth factor-1 hormonal axis.[29–33] Our observation of post-pubertal boys having more height z scores decreased during therapy than post-pubertal girls (Table 3) suggested a reduction in the production of free testosterone associated with TKI treatment,[34] a speculation remained to be investigated in the future studies.

Among the controls, post-pubertal patients showed more height z score decrease than pre-pubertal patients and lacked catch-up growth after completion of therapy

Clinical characteristics	Diagnosis		End of therapy		△Height Z Scores[a] Median (Range)	P value	P value[b]
	No.	Median height Z Score	No.	Median height Z Score			
Pre-pubertal vs. post-pubertal							
Pre-pubertal	101	0.08	101	−0.69	−0.88 (−4.25, 1.47)		
Female	26	0.10	26	−0.91	−1.22 (−4.25, 1.47)	0.14	0.89
Male	75	0.08	75	−0.69	−0.82 (−3.04, 1.46)		
Post-pubertal	39	0.01	39	−0.84	−0.88 (−2.40, 0.67)		
Female	13	−0.99	13	−1.03	−0.76 (−2.27, 0.67)	**0.02**	
Male	26	0.40	26	−0.68	−1.07 (−2.40, 0.16)		
Sex							
Female	39	−0.06	39	−0.99	−0.85 (−4.25, 1.47)		
Pre-pubertal	26	0.10	26	−0.91	−1.22 (−4.25, 1.47)	0.07	0.98
Post-pubertal	13	−0.99	13	−1.03	−0.76 (−2.27, 0.67)		
Male	101	0.02	101	−0.69	−0.88 (−3.04, 1.46)		
Pre-pubertal	75	0.08	75	−0.69	−0.82 (−3.04, 1.46)	0.11	
Post-pubertal	26	0.40	26	−0.68	−1.07 (−2.40, 0.16)		

Note: P values less than 0.05 showed in bold. [a]△Height z scores indicate height z scores at the end of therapy minus height z scores at diagnosis. [b]Comparisons of △Height z scores across pubertal age and sex group.

***Table 3*: Height loss between at diagnosis and at the end of therapy in 140 tyrosine kinase inhibitor treated Ph+ ALL patients classified by age group and sex.**

(Supplemental Fig. S1), a finding consistent with our previous study.[7] However, between the end of therapy and 1-year off therapy, our controls overall recovered more height z scores than the TKI-treated patients, a finding suggesting that the increase in the height z score in the controls was likely contributed by the pre-pubertal patients. Longer follow-up is needed to determine if the longitudinal growth will improve in our TKI-treated patients, especially males, after cessation of therapy which removes the suppressive effect of TKI on the testosterone production in both pre-pubertal and post-pubertal patients.

There are several limitations of this study. First, based on the recommendation of the data and safety monitoring committee, several patients who were receiving imatinib were switched to receive dasatinib for the remaining of the treatment. Since the switch in therapy occurred at different phases of treatment, it was not feasible to account for their different treatment duration and cumulative dosage of TKI in the analyses. We believe that the switch in the treatment group in these few patients would not affect the overall results of the study because the adverse impact of dasatinib and imatinib on height was similar for most of the patients who did not switch the treatment. Second, protocol deviation occurred in 25 (17.9%) of the 140 TKI-treated patients who continued to receive TKI beyond the end of continuation treatment. Even though they were censored at the time of cessation of continuation treatment, these occurrences could still impact the strength of this study. Third, because of the lack of resources, we were not able to collect and analyze data on the dose intensity of TKI treatment such as actual days or dosages of administration as well as the Tanner Stage of development. Fourth, results of subgroup analyses should be interpreted with caution due to relatively small sample size. A goal of this study is also to observe if there is any signal of TKI-induced growth inhibition in patient subgroups. To maintain reasonable statistical power for this goal, we did not make adjustment for multiple comparisons. Findings on subgroups should be confirmed by designed prospective studies. Finally, our data base did not capture supportive care measure used during chemotherapy treatment which can alter the blood levels of the TKI,[35] and this factor could not be included in our analyses.

Contributors

JC collated data, conducted data analysis, and drafted the manuscript. HL, YC, JY, JG, HJ, XZ, XJ, XW, NW, XT, CL, YF, FZ, HL, LS, LY, JG, AL, C.-KL, and YZ contributed to preliminary data collation. JT, JJY, and SS contributed to writing the manuscript. CC supervised data analysis. C-HP conceived of the project, directed the research, and drafted the manuscript. All authors approved the final version of the manuscript.

Data sharing statement

Deidentified participant data are available by contacting Dr. Jiaoyang Cai (caijiaoyang@scmc.com.cn).

Declaration of interests

C-HP is on the scientific advisory board of Adaptive Biotechnology and the Data Monitoring Committee of Novartis; and has received honorarium from Amgen. JJY receives research funding from Takeda Pharmaceutical and AstraZeneca Company. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100818.

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