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High Incidence of Vertebral Fractures in Children with Acute Lymphoblastic Leukemia 12 Months After the Initiation of Therapy

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Abstract

Purpose—Vertebral fractures due to osteoporosis are a potential complication of childhood acute lymphoblastic leukemia (ALL). To date, the incidence of vertebral fractures during ALL treatment has not been reported.

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Patient and Methods—We prospectively evaluated 155 children with ALL during the first 12 months of leukemia therapy. Lateral thoracolumbar spine radiographs were obtained at baseline and 12 months. Vertebral bodies were assessed for incident vertebral fractures using the Genant semi-quantitative method, and relevant clinical indices such as spine bone mineral density (BMD), back pain and the presence of vertebral fractures at baseline were analyzed for association with incident vertebral fractures.

Results—Of the 155 children, 25 (16%, 95% Confidence Interval (CI) 11% to 23%) had a total of 61 incident vertebral fractures, of which 32 (52%) were moderate or severe. Thirteen of the 25 children with incident vertebral fractures (52%) also had fractures at baseline. Vertebral fractures at baseline increased the odds of an incident fracture at 12 months by an odds ratio of 7.3 (95% CI 2.3 to 23.1, $p = 0.001$). In addition, for every one standard deviation reduction in spine BMD Z-score at baseline, there was 1.8-fold increased odds of incident vertebral fracture at 12 months (95% CI 1.2 to 2.7, $p = 0.006$).

Conclusion—Children with ALL have a high incidence of vertebral fractures after 12 months of chemotherapy, and the presence of vertebral fractures and reductions in spine BMD Z-scores at baseline are highly associated clinical features.

Keywords

acute lymphoblastic leukemia; children; osteoporosis; vertebral fractures

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most frequent pediatric cancer, with risk-targeted treatment regimens curing ALL in more than 80% of patients.[1] Fractures due to osteoporosis are an important complication of childhood leukemia at diagnosis, as well as during and after ALL therapy.[2–10] We recently found that 16% of children with recently diagnosed ALL had vertebral fractures, and that half of the children manifested moderate or severe fractures. Furthermore, each standard deviation (SD) reduction in spine bone mineral density (BMD) Z-score was associated with an 80% increased odds of vertebral fractures.[11]

To date, the incidence of vertebral fractures following the initiation of chemotherapy has not been reported. This is an important consideration since children with ALL receive osteotoxic medications such as glucocorticoids and methotrexate, both of which may further compromise bone strength.[12] In the present study, we describe the incidence of vertebral fractures in children with ALL in the year after chemotherapy initiation and evaluate the associated clinical factors.

SUBJECTS AND METHODS

Patients and Study Design

Patients were recruited through pediatric oncology clinics in 10 children's hospitals across Canada as part of the **ST**eroid-associated **O**steoporosis in the **P**ediatric **P**opulation (**STOPP**) research program. Children from one month to 17 years of age with ALL were enrolled (N = 188) from 2005 to 2007, with the baseline bone health assessment initiated within 30 days of

glucocorticoid therapy.[11] The study was approved by the Ethics Board in each institution and informed consent/assent were obtained, as appropriate. Children were excluded from the study if they had received treatment with a bisphosphonate or calcium and vitamin D supplementation that exceeded the Dietary Reference Intake for age.[11]

Clinical Data

All children were treated according to Children's Oncology Group (nine sites) or the Dana Farber Cancer Institute (one site) protocols. Clinical data were obtained at baseline and every three months following the baseline assessment for a total of 12 months. Height, weight and pubertal staging according to Marshall and Tanner, [13,14] were determined as previously described.[11] Height, weight, and body mass index (weight (kg) divided by height (meters^2)) raw values were transformed into age- and gender-matched Z-scores according to the United States Centers for Disease Control National Center for Health Statistics normative database[15]; for children younger than two years, body mass index Z-scores were calculated according to the World Health Organization child growth standards.[16] The presence or absence of back pain reported by the participant was recorded at each study visit, and the spine was palpated for tenderness at baseline and at 12 months. For non-verbal children, the history of back pain was obtained from the caregiver.

Dietary calcium and vitamin D intake were assessed by a validated food frequency questionnaire.[17] Daily intake (diet plus supplement) was expressed as the percent of the Adequate Intake value based on Dietary Reference Intakes.[18] The percentage of adequate intake scores were then classified as <50% of the age-related Dietary Reference Intake, ≥50 and < 100%, or ≥100% of the Reference Intake. Physical activity was assessed through the Habitual Activity Estimation Scale.[11,19,20]

Quantification of Glucocorticoid and Methotrexate Exposure

The dose of systemic glucocorticoid therapy (oral and intravenous) received during the 12 month observation period was converted into prednisone equivalents expressed as:[21–23] (1) cumulative glucocorticoid dose, the amount in prednisone equivalents (mg/m^2) received during the observation period; (2) average glucocorticoid dose, the cumulative dose in prednisone equivalents divided by the total number of days during the observation period; and (3) glucocorticoid dose intensity, the cumulative dose in prednisone equivalents, divided by the number of days in receipt of steroids during the observation period. Methotrexate was quantified by summing the cumulative dose over the observation period.

Vertebral Fracture Assessment

Lateral thoracolumbar spine radiographs were obtained at baseline and 12 months, with vertebral fracture assessment based on the Genant semi-quantitative method from T4 to L4.[24] Vertebral bodies were graded according to the extent of the difference in height ratios from 100% when the anterior vertebral height was compared to the posterior height, the middle height to the posterior height, and the posterior height to the posterior height of adjacent vertebral bodies. The scores corresponded to the following differences in height ratios: Grade 0: 20% or less (normal); Grade 1 fracture (mild): > 20 to 25%; Grade 2 fracture (moderate): > 25 to 40%; Grade 3 fracture (severe): > 40%. Minimal physiological

rounding of vertebral bodies in the mid-thoracic region of the spine, as can be seen in normal children, was assigned a Grade 0 score.[25,26] An incident vertebral fracture was defined as an increase in the Genant grade of at least one compared with baseline.

Lumbar Spine BMD by Dual-Energy X-Ray Absorptiometry, Bone Age and Second Metacarpal Morphometry

BMD was measured in the anterior-posterior direction at the lumbar spine (L1-L4) by dual-energy x-ray absorptiometry using either Hologic (Hologic, Bedford, MA; QDR 4500, three centers; Discovery, two centers; Delphi, one center) or Lunar Prodigy (GE Lunar Corporation, Madison, WI; four centers) systems at baseline and at 6 and 12 months. Machines were cross-calibrated as previously described.[11] Data were converted to Hologic units and Z-scores were generated using the Hologic 12.4 normative database, a database provided by the manufacturer that spans the age ranges included in this study. Radiographs of the left hand and wrist were obtained at baseline and 12 months to determine bone age and second metacarpal percent cortical area, as previously reported.[11]

Statistical Analyses

Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using mean and standard deviation (SD) or median (25^{th} percentile, 75^{th} percentile or minimum, maximum). The 95% Confidence Intervals (CI) for the proportions of patients with vertebral deformities were calculated using the Wilson score method.[27]

Differences between those with and without incident vertebral fracture were assessed using a chi-square or Fisher's exact test for categorical variables and a Student's t-test or a non-parametric (Wilcoxon Mann-Whitney) test for continuous variables, as appropriate. Multivariable logistic regression was performed to identify clinical variables significantly associated with incident vertebral fracture after adjusting for the variables in the model. To address overfitting of models, the variables included in the models were identified using a two step process. First, the variables that were statistically significant based on univariate testing were assessed. This first step considered at least 5 events per variable, an approach supported by Vittinghoff and McCulloch. [28] The second step was to add non-significant but nevertheless clinically important variables, to demonstrate that such covariates were considered in the models. Vittinghoff and McCullogh[28] found a low risk of bias with 5 to 9 events per outcome variable in logistic regression models and this formed the basis for the sample size used for the models in this article.

For the models that included vertebral fractures in children at baseline as a predictor variable, covariance analysis was used. Model discrimination was assessed using the c statistic (equivalent to the area under the receiver operating characteristic curve), which refers to the ability of the model to distinguish between those children having a higher risk of sustaining incident vertebral fractures versus those with lower risk.[29] The c statistic between 0.7 and 0.8 is consistent with acceptable model discrimination; 0.8 to 0.9 is an indication of excellent discrimination. Reported p values are two-sided and a p-value < 0.05

was considered statistically significant. Analyses were conducted using SPSS 18.0 (SPSS Inc., Chicago IL).

RESULTS

Clinical Characteristics of the Cohort

A total of 368 children were approached for participation in the study; 161 declined and 19 were excluded because of failure to undergo a bone health evaluation within the baseline timeline. Of these 188 children, 155 completed follow-up to 12 months (Table 1). The reasons for lack of available data on 33 children at 12 months are presented in Figure 1. The clinical profile at baseline for the 33 children without data at 12 months did not differ significantly from those with complete follow-up (data not shown).

For the 155 children who completed 12 month data collection, the baseline spine BMD was carried out at a median of 15 days from glucocorticoid initiation (inter-quartile range (IQR): 5, 22) and the baseline spine radiograph was carried out at a median of 20 days (IQR: 10.5, 25.5). Children with prevalent vertebral fractures at baseline (N = 25) had a similar number of days between glucocorticoid initiation and the spine radiograph (median 20 days; IQR 6.5, 26) compared with those without baseline vertebral fractures (median 19.5 days, IQR 11.25, 25, $p = 0.642$). Similarly, the cumulative glucocorticoid dose up until the time of the baseline spine radiograph was similar for children with baseline vertebral fractures (median 890 mg/m^2, IQR 200, 1064) compared with those without (median 877 mg/m^2, IQR 514, 1134; $p = 0.369$). The percentage of children in Tanner Stage 1 pubertal development at 12 months was 76%, with 24% in Stages 2 to 5. Mean height Z-scores were lower at 12 months (mean ± SD = −0.1± 1.2) compared with baseline (0.3 ± 1.2, $p < 0.001$) whereas weight Z-scores were higher (0.5 ± 1.2 at 12 months versus 0.4 ± 1.3 at baseline, $p = 0.03$), resulting in increased body mass index Z-scores (0.9 ± 1.1 at 12 months versus 0.4 ± 1.5 at baseline, $p < 0.001$).

Vertebral Fractures

Twenty-five of the 155 children (16%, 95% CI 11% to 23%; 14 boys) sustained 61 incident vertebral fractures. None reported trauma. Fifty-two (85%) of the 61 incident vertebral fractures were in previously normal vertebral bodies, whereas nine were worsening of existing fractures. Twelve children (48%) had mild fractures as the worst grade, eight (32%) had moderate fractures and five (20%) sustained severe incident fractures. Representative fractures are shown in Figures 2A and 2B. Thirteen children (52%) had a single vertebral fracture, seven had two to three fractures (28%) and five children had four to ten incident fractures (20%). These five children had 31 (51%) of the total number of incident fractures. Fractures were clustered in the mid-thoracic region (38% from T5 to T7) and thoracolumbar junction (21% from T12 to L2) and 52% of the incident vertebral fractures were moderate or severe.

Differences in the Clinical Profiles of Children With and Without Incident Vertebral Fractures (Table 2)

The two groups did not differ significantly in age, gender, anthropometry, methotrexate or glucocorticoid exposure, leukemia immunophenotype or risk category, white blood count, physical activity, second metacarpal percent cortical area Z-score, or total calcium and vitamin D intake. However, over 50% of children with incident vertebral fractures had fractures at baseline. Furthermore, the 13 children with both incident fractures as well as prevalent fractures at baseline carried most of the 12-month incident fracture burden, harbouring 45/61 (74%) of the incident fractures. The percentage of children with incident fractures was highest among those with more severe fractures at baseline: 12/130 children (9%) without fractures at baseline had incident vertebral fractures at 12 months compared with 5/11 children (45%) with Grade 1 fractures, 4/9 children (44%) with Grade 2 fractures and 4/5 children (80%) with Grade 3 fractures ($p < 0.001$).

The mean spine BMD Z-score was significantly lower in children with incident vertebral fractures compared with those without at baseline and at 6 and 12 months (Figure 3). The mean change in spine BMD Z-score was similar between the two groups from baseline to 12 months (Table 2); however, children with incident vertebral fractures had greater increases in spine BMD Z-scores between six and 12 months.

Clinical Variables Associated with Increased Odds of Incident Vertebral Fracture

Logistic regression models were fit to examine factors associated with increased odds of incident vertebral fracture at 12 months for the entire cohort (Models 1 through 3; n=155) and for the subset of children who did not have vertebral fractures at baseline (Model 4; n=130). For all models, the dependent variable was a yes/no indicator defined as yes for children who had at least one incident vertebral fracture at 12 months.

The results of Model 1 (Figure 4) show the presence of at least one vertebral fracture at baseline was highly associated with increased odds of a child sustaining at least one incident vertebral fracture at 12 months (c statistic = 0.78, 95% CI 0.67 to 0.90). Other variables included in this model were spine BMD Z-score, back pain and age (all at baseline) as well as gender and cumulative glucocorticoid dose. Model 2 (c statistic = 0.74, 95% CI 0.63 to 0.85) was generated by excluding vertebral fractures at baseline from Model 1. In this model, baseline spine BMD Z-score was associated with increased odds of incident vertebral fracture, as follows: for every one SD reduction in spine BMD Z-score at baseline, the odds of incident vertebral fracture increased 1.8-fold (95% CI 1.2 to 2.7, $p = 0.006$). In Model 3 (c statistic = 0.78, 95% CI 0.67 to 0.90), the presence of vertebral fractures at baseline was replaced with the highest Genant Grade at baseline. Both the presence of Grade 1 vertebral fractures (odds ratio 7.6, 95% CI 1.8 to 31.8, $p = 0.006$) and the presence of Grade 2/3 fractures (odds ratio 7.0, 95% CI 1.6 to 30.2, $p = 0.009$) were associated with an increased odds of sustaining at least one incident vertebral fracture.

The fourth model (c statistic = 0.81, 95% CI 0.68 to 0.94) assessing factors associated with incident vertebral fracture in the 130 children who did not have vertebral fractures at baseline showed that among spine BMD Z-score at baseline, change in body mass index

from baseline to 12 months, back pain reported after baseline, age, gender and cumulative glucocorticoid dose, back pain was associated with 9.2-fold increased odds of incident vertebral fractures (95% CI 1.6 to 51.7, $p = 0.012$). Children with incident vertebral fractures in the absence of fractures at baseline had greater increases in body mass index Z-scores from baseline to 12 months compared with those without fractures at either time point (mean ± SD = +1.1 ± 1.5 versus +0.5 ± 0.9, $p = 0.043$).

DISCUSSION

We found that 16% of children with ALL developed incident vertebral fractures 12 months following the initiation of therapy. The presence of low spine BMD Z-score or vertebral fractures of any grade were associated with significantly increased odds of incident vertebral fractures. That an initial vertebral fracture is associated with increased odds of a subsequent fracture has not been previously reported in children. However, the phenomenon is well-known among adults,[30,31] described as the so called “vertebral fracture cascade”.[32] Among post-menopausal women, vertebral fracture at an initial timepoint is associated with five-fold increased relative risk for incident vertebral fracture 12 months later.[31] Our observation that every one SD reduction in spine BMD Z-score at baseline was associated with an 80% increased odds of incident vertebral fracture is also aligned with adult studies.[33,34]

Our results did not show a relationship between glucocorticoid or methotrexate dose and incident vertebral fracture. Retrospective studies in pediatric ALL have shown a relationship between these agents and skeletal morbidity after five to ten years of follow-up,[3,6,35] including an increase in long-bone fractures.[4] Interestingly, in our study the children with incident vertebral fractures in the absence of fractures at baseline had greater increases in body mass index over the 12 month period, an observation that suggests clinically important variability in glucocorticoid sensitivity mediated by differences in glucocorticoid pharmacokinetics or pharmacogenomics among patients.[36] The absence of a link to glucocorticoid or methotrexate dose in our study could also reflect the relatively small number of children with vertebral fractures, particularly in view of the standardized chemotherapy protocols. Similarly, we did not find any differences in leukemia variables (such as white blood count) for children with incident vertebral fractures compared with those without, an observation that could also have been impacted by sample size.

That a sub-set of children had a disproportionate number of prevalent fractures at baseline plus incident fractures at 12 months raises the possibility of genetic susceptibility to bone fragility in these particular children. Our data also suggest that the determinants of compromised bone strength leading to fracture may be different early in the course of leukemia therapy compared to later. At ALL diagnosis, bone fragility has been linked to excessive skeletal resorption through liberation of osteoclast-activating factors by the leukemic cells (including interleukins 6 and 8).[37] This observation is supported by our data showing excessive osteolysis on the second metacarpal endosteal surface among children with vertebral fractures and recently diagnosed ALL, resulting in reduced metacarpal cortical width.[11] Vassilopoulou-Sellin and Ramirez [38] reported a young ALL patient with back pain and subtle vertebral changes at diagnosis followed by severe vertebral fractures just two months later. A trans-iliac bone biopsy showed signs of prior, accelerated resorption

that had resolved by 2 months. Our data showing that children with incident vertebral fractures at 12 months had greater increases in spine BMD Z-scores between 6 and 12 months also suggests the 12-month incident vertebral fractures may have occurred early in the observation period, and were then followed by a degree of recovery manifesting as enhanced BMD accrual. In contrast, studies that have shown a relationship between glucocorticoid exposure and skeletal morbidity after five to ten years of follow-up[3,6,35] suggest that medication-induced osteotoxicity may take time to manifest clinically.

A key clinical question is whether children with ALL and vertebral fractures in the first year of therapy should be treated with osteoporosis agents such as bisphosphonates. To date, there have been no randomized, placebo-controlled trials in pediatric ALL to provide adequate safety and efficacy data and thereby justify the use of such agents as standard of care. It is possible that bisphosphonates could treat the low BMD and also stabilize vertebral fractures in this context by inflencing the early ALL effects on the skeleton, just as bisphosphonates are effective in the cytokine-induced bone disease of multiple myeloma.[39] If later adverse bone manifestations in ALL are chemotherapy-related, bisphosphonates might also be effective, as their benefits are well-documented in the treatment of adult glucocorticoid-induced osteoporosis.[39] It will be important that any future osteoporosis treatment studies in pediatric ALL consider that the mechanisms underlying bone disease may be different early after disease presentation compared with later or even after completion of chemotherapy.

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Abbreviations

ALL	Acute lymphoblastic leukemia
BMD	Bone mineral density
CI	Confidence interval
IQR	Inter-quartile range
SD	Standard deviation

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The Canadian STeroid-associated Osteoporosis in the Pediatric Population (STOPP) Consortium (a pan-Canadian, pediatric bone health working group)

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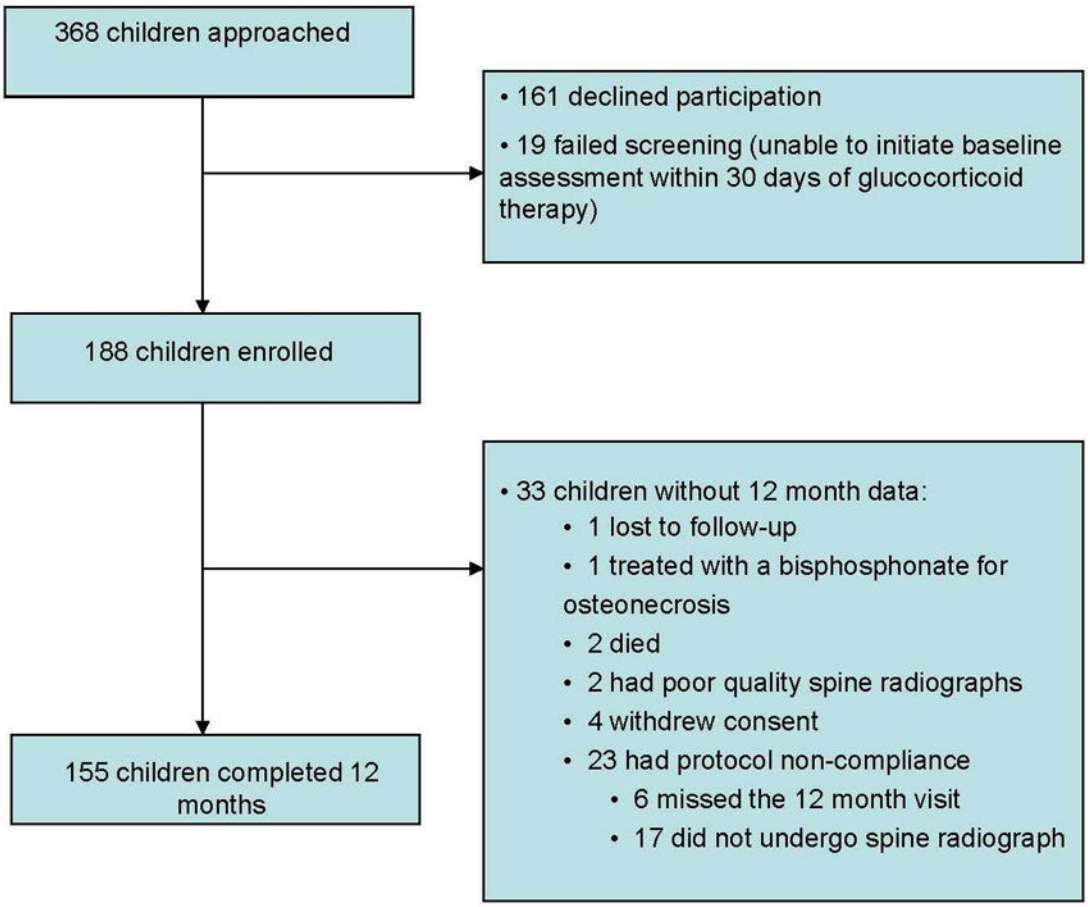

Figure 1.
Disposition of patients from baseline to 12 months with reasons for lack of available data on 33 children at 12 months.

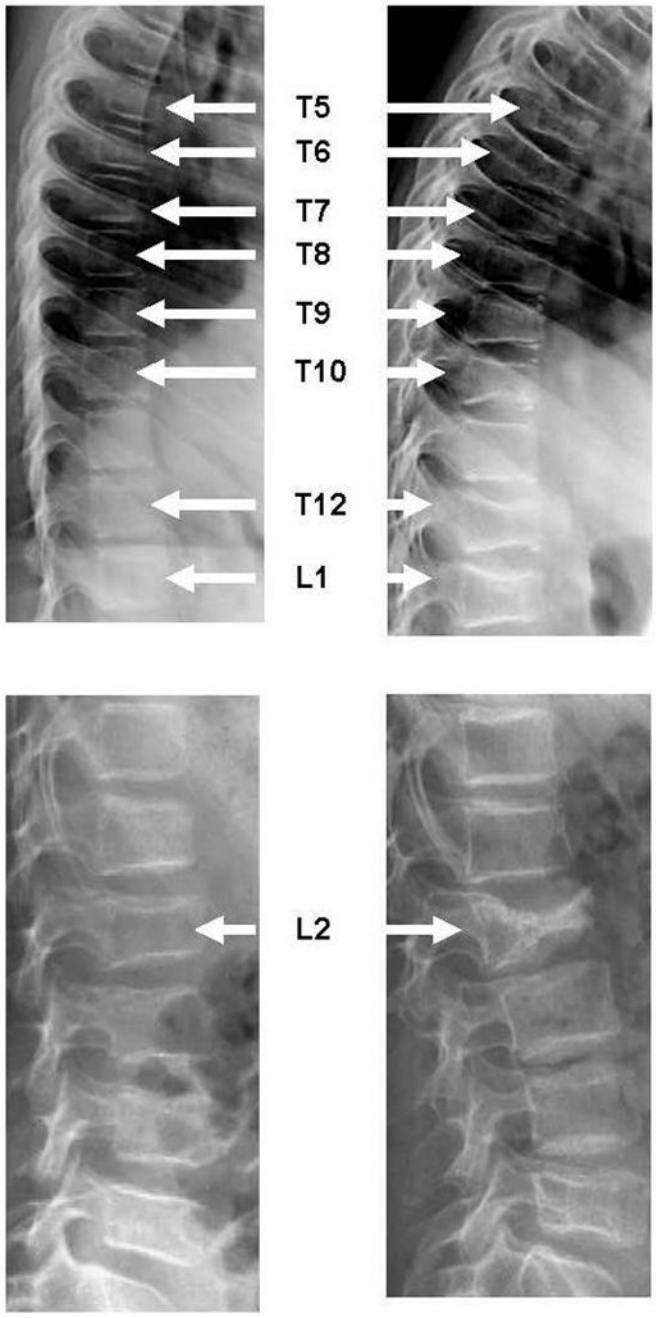

Figure 2.

Representative incident vertebral fractures at 12 months following initiation of therapy for pediatric ALL. (A) left panel shows a 9 year old girl at baseline with a normal spine radiograph. At 12 months (right panel), she has multiple incident vertebral fractures (a severe fracture at T5, moderate fractures at T10, T12 and L1, and mild fractures at T6, T7, T8 and T9). (B) left panel shows a 9 year old boy at baseline with a moderate L2 fracture. At 12 months (right panel), the L2 deformity has progressed to a severe fracture.

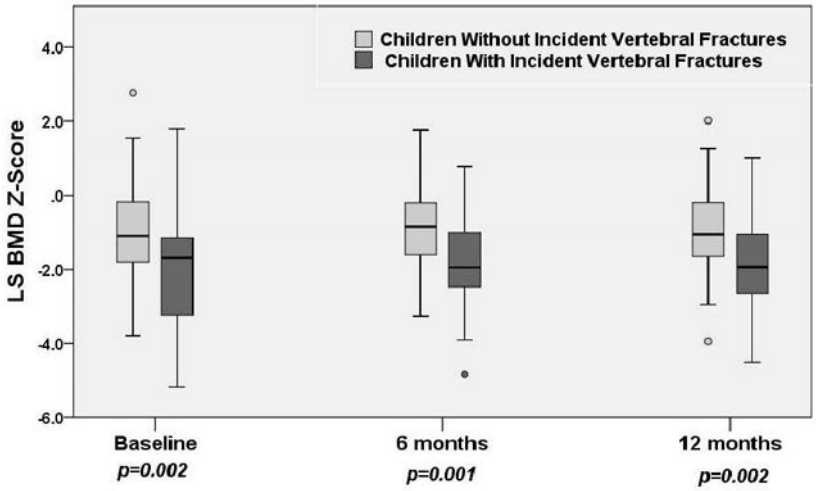

Figure 3.

The median (with 25th and 75th percentiles) lumbar spine BMD Z-scores at baseline, 6 and 12 months post-initiation of therapy for children with and without incident vertebral fractures.

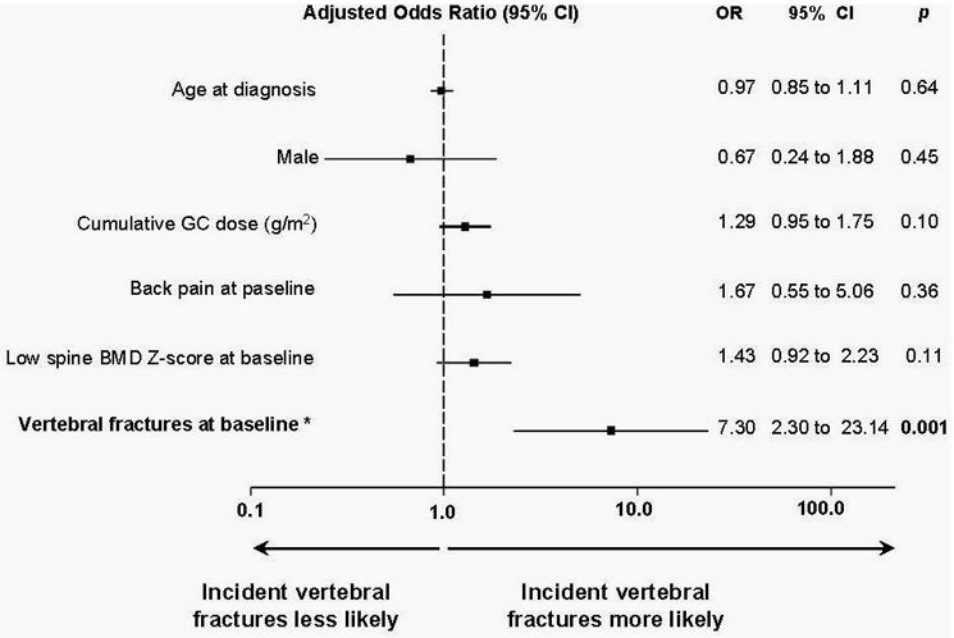

Figure 4.

Results of logistic regression model 1 showing that the presence of at least one vertebral fracture at baseline was highly associated with increased odds of a child sustaining at least one incident vertebral fracture at 12 months. BMD, bone mineral density; GC, glucocorticoid; OR, odds ratio.

Table 1

Clinical Characteristics of the Children with Acute Lymphoblastic Leukemia 12 Months After the Initiation of Therapy

Clinical Characteristics	N=155 *
Demographic Data	
Male, N (%)	91 (59)
Age at 12 months (years), median (min, max)	6.4 (2.2, 18.0)
Bone Age at 12 months (years), median (min, max)	5.8 (2.0, 18.5)
Diagnosis, N (%)	
Pre-B-cell acute lymphoblastic leukemia	141 (91)
T-cell acute lymphoblastic leukemia	14 (9)
Leukemia protocol, N (%)	
Dana Farber	33 (21)
Children's Oncology Group	122 (79)
Leukemia risk category, N (%)	
Standard Risk	96/153 (63)
High Risk	57/153 (37)
Anthropometry, mean (SD)	
Δ Height Z-score from baseline to 12 months	−0.4 (0.5)
Δ Weight Z-score from baseline to 12 months	0.1 (0.7)
Δ BMI ** Z-score from baseline to 12 months	0.5 (1.0)
Lumbar Spine Bone Mineral Density, mean (SD)	
LS BMD Z-score at baseline	−1.2 (1.3)
Δ LS BMD Z-score from baseline to 12 months	0.1 (0.9)
Vitamin D and Calcium Intake	
Average daily vitamin D intake ***, N (%)	
< 50 %	25/123 (20)
50 – <100 %	63/123 (51)
>= 100%	35/123 (29)
Average daily calcium intake ***, N (%)	
< 50 %	5/124 (4)
50 – <100 %	11/124 (9)
>= 100%	108/124 (87)

* For data expressed as percentages, the denominator is 155 children unless otherwise specified

** BMI = Body mass index

*** Combined dietary plus supplemental intake, expressed as the % of the Dietary Reference Intake for age

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Table 2

Comparison of Children With and Without Incident Vertebral Fractures at 12 Months According to the Genant Semi-Quantitative Method

Clinical Characteristics	Children without Incident Vertebral Fractures at 12 Months N=130*	Children with Incident Vertebral Fractures at 12 Months N=25*	*p*
Demographic Data			
Male, N (%)	77 (59)	14 (56)	0.76[A]
Age at 12 months (years), median (min, max)	6.2 (2.2, 18.0)	6.7 (3.1, 15.5)	0.69[B]
Anthropometry, mean (SD)			
Height Z-score at baseline	0.3 (1.2)	0.1 (1.2)	0.37[C]
Δ Height Z-score from baseline to 12 months	−0.4 (0.4)	−0.4 (0.6)	0.98[C]
Weight Z-score at baseline	0.5 (1.3)	0.1 (1.2)	0.14[C]
Δ Weight Z-score from baseline to 12 months	0.1 (0.6)	0.3 (0.9)	0.23[C]
BMI** Z-score at baseline	0.4 (1.5)	0.0 (1.6)	0.17[C]
Δ BMI Z-score from baseline to 12 months	0.5 (0.9)	0.7 (1.4)	0.44[C]
History of Prevalent Vertebral Fractures			
Children with vertebral fractures at baseline, N (%)	12 (9)	13 (52)	**<0.001**[A]
Back Pain			
Back pain by report at baseline (yes), N (%)	30 (23)	13 (52)	**0.003**[A]
Back pain by report after baseline (yes), N (%)	53 (41)	15 (60)	0.08[A]
Back pain by palpation after baseline (yes), N (%)	3/121 (3)	2/24 (8)	0.19[A]
Lumbar Spine BMD, mean (SD)			
Δ Spine BMD Z-score from baseline to 6 months	0.1 (0.8)	0.1 (0.9)	0.95[C]
Δ Spine BMD Z-score from 6 to 12 months	0.0 (0.6)	0.3 (0.5)	**0.02**[C]
Δ Spine BMD Z-score from baseline to 12 months	0.0 (0.8)	0.3 (1.1)	0.19[C]
Glucocorticoid Exposure (Total and Dexamethasone Alone)			
Cumulative glucocorticoid dose (mg/m^2), median (IQR)	4017 (3455, 4446)	3984 (3371, 4407)	0.90[B]
Average glucocorticoid dose (mg/m^2/day), median (IQR)	10.2 (9.0, 11.3)	10.3 (8.6, 11.4)	0.90[B]
Glucocorticoid dose intensity (mg/m^2/day), median (IQR)	45.5 (42.9, 53.9)	45.0 (39.7, 49.9)	0.25[B]

Clinical Characteristics	Children without Incident Vertebral Fractures at 12 Months N=130*	Children with Incident Vertebral Fractures at 12 Months N=25*	p
Cumulative dexamethasone dose (mg/m^2), median (IQR)	3419 (2187, 4229)	3197 (1047, 4141)	0.15[B]
Methotrexate Exposure			
Cumulative methotrexate dose (mg/m^2), median (IQR)	1330 (705, 5619)	1243 (721, 5488)	0.99[B]

*For data expressed as percentages, the denominators are 130 for children without incident vertebral fractures and 25 for children with incident fractures unless otherwise indicated.

**BMI = body mass index.

[A]Statistical significance determined by Chi-square or Fisher's Exact test;

[B]Statistical significance determined by Wilcoxon Mann-Whitney test;

[C]Statistical significance determined by Student's t-test.