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Incident Vertebral Fractures in Children with Leukemia During the Four Years Following Diagnosis

Elizabeth A Cummings¹, Jinhui Ma², Conrad V Fernandez¹, Jacqueline Halton², Nathalie Alos³, Paivi M Miettunen⁴, Jacob L Jaremko⁵, Josephine Ho⁴, Nazih Shenouda², Mary Ann Matzinger², Brian Lentle⁶, David Stephure⁴, Robert Stein⁷, Ann Marie Sbrocchi⁸, Celia Rodd⁹, Bianca Lang¹, Sara Israels⁹, Ronald M Grant¹⁰, Robert Couch⁵, Ronald Barr¹¹, John Hay¹², Frank Rauch⁸, Kerry Siminoski⁵, Leanne M Ward², and the Canadian STOPP Consortium¹³

¹Dalhousie University, Halifax, NS, Canada

²University of Ottawa, Ottawa, ON, Canada

³Université de Montréal, Montreal, QC, Canada

⁴University of Calgary, Calgary, AB, Canada

⁵University of Alberta, Edmonton, AB, Canada

⁶University of British Columbia, Vancouver, BC, Canada

⁷University of Western Ontario, London, ON, Canada

⁸McGill University, Montréal, QC, Canada

⁹University of Manitoba, Winnipeg, MB, Canada

¹⁰University of Toronto, Toronto, ON, Canada

¹¹McMaster University, Hamilton, ON, Canada

¹²Brock University, St. Catharines, ON, Canada

Abstract

Objectives—The purpose of this article was to determine the incidence and predictors of vertebral fractures (VF) during the four years following diagnosis in pediatric acute lymphoblastic leukemia (ALL).

Patients and Methods—Children were enrolled within 30 days of chemotherapy initiation, with incident VF assessed annually on lateral spine radiographs according to the Genant method. Extended Cox's models were used to assess the association between incident VF and clinical predictors.

Corresponding Author: Dr. Leanne Ward, MD, FRCPC, Associate Professor, Pediatrics, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, Canada, K1H 8L1, Tele: 613 737 2253, Fax: 613 738 4211, Lward@cheo.on.ca.

¹³National Pediatric Bone Health Working Group

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Results—186 children with ALL completed the baseline evaluation (median age 5.3 years, interquartile range 3.4 to 9.7, 58% boys). The VF incidence rate was 8.7 per 100 person-years, with a four-year cumulative incidence of 26.4%. The highest annual incidence occurred at 12 months (16.1%; 95% confidence interval (CI) 11.2 – 22.7), falling to 2.9% at four years (95% CI, 1.1 – 7.3). Half of the children with incident VF had moderate or severe VF and 39% of those with incident VF were asymptomatic. Every 10 mg/m² increase in average daily glucocorticoid dose (prednisone equivalents) was associated with a 5.9-fold increased VF risk (95% CI, 3.0–11.8; $p < 0.01$). Other predictors of increased VF risk included: VF at diagnosis, younger age, and lower spine bone mineral density Z-scores at baseline and each annual assessment.

Conclusions—One quarter of children with ALL developed incident VF in the four years following diagnosis; most of the VF burden was in the first year. Over one third of children with incident VF were asymptomatic. Discrete clinical predictors of VF were evident early in the patient's clinical course, including VF at diagnosis.

Key Terms

Incident vertebral fractures; Acute lymphoblastic leukemia; Glucocorticoids; Osteoporosis; Children

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, with over 80% cured with current treatment strategies (1). Skeletal morbidity has long been recognized as a complication of ALL and its treatment, occurring at diagnosis, during treatment, and also after chemotherapy (2–7). At diagnosis, skeletal abnormalities are evident on plain radiographs in up to 75% of children (8), including metaphyseal lucencies and extremity fractures (2, 8–10). The prevalence of osteoporosis at ALL diagnosis manifesting as low trauma extremity fractures ranges from three to 10% based on retrospective (8, 11, 12) and prospective (13) studies. Almost half of children with ALL have musculoskeletal pain at presentation and many have difficulty walking (13, 14). Bone fragility at ALL diagnosis has been linked to increased osteoclast-mediated bone resorption resulting from cytokines released by leukemic cells (15).

Vertebral fractures (VF) are another important clinical manifestation of osteoporosis in children with ALL (5, 6). We recently reported the results of a prospective VF surveillance study which showed that VF occur even more frequently than non-VF, affecting 16% of children in our cohort at diagnosis (5). A further 16% of children sustained incident (i.e., new) VF in the 12 months following chemotherapy initiation (6). We also found that the skeletal phenotype at diagnosis (prevalent VF and low bone mineral density (BMD) Z-scores) predicted incident VF in the next 12 months. Of note, VF are frequently asymptomatic (including moderate and severe compression) (5, 6), and therefore go undetected in the absence of systematic surveillance.

A number of questions about the longer-term natural history and clinical predictors of VF in pediatric ALL remain unanswered. For example, it is unknown whether incident VF occur beyond the first 12 months of chemotherapy, and at what time point VF risk is highest.

Questions also remain about the severity of long-term bone morbidity due to VF, and the risk factors for incident VF in the years following diagnosis. Understanding these issues will be instrumental in developing evidenced-based spine health monitoring and management strategies in this patient population. The aim of this report is to describe the annual and cumulative incidence and predictors of VF during the four years following diagnosis of pediatric ALL.

Patients and Methods

Patients were recruited through pediatric oncology clinics in 10 Canadian children's hospitals as part of the STeroid-Associated Osteoporosis in the Pediatric Population (STOPP) research program. Children from one month to 17 years of age with ALL were enrolled between 2005 and 2007, and had the baseline bone health assessment within 30 days of chemotherapy initiation (5). The eligibility criteria for enrolment in the STOPP study have been previously described (5, 6). The study was approved by each institutional ethics board and informed consent/assent was obtained, as appropriate.

Clinical Data

Clinical data were obtained at baseline and then prospectively every three months for four years (including an anticipated period of 1.5 years following chemotherapy cessation in girls, and six months following chemotherapy cessation in boys). Height, weight, leukemia risk category and pubertal staging according to Marshall and Tanner (16, 17) were determined as previously described (5, 6). Height, weight, and body mass index (BMI) raw values were transformed into age- and sex-matched Z-scores according to the United States Centers for Disease Control National Center for Health Statistics normative database (18); for children younger than two years, BMI Z-scores were calculated according to the World Health Organization child growth standards (19). Body surface area square meters was calculated as $\sqrt{\text{weight}(\text{kg}) \times \text{height}(\text{cm})/3600}$. The presence or absence of back pain reported by the participant, or by the caregiver of non-verbal children, was recorded at each 3 month study visit. Dietary calcium and vitamin D intake were assessed by a validated food frequency questionnaire every three months (20), with calcium and vitamin D intake by supplementation added to estimate total daily intakes. Intake was further classified as <50%, 50–100%, and >100% of the age-related Dietary Reference Intake (21). Physical activity was assessed every three months using the Habitual Activity Estimation Scale (22, 23), as described previously (5, 6). Methotrexate exposure was expressed as the average weekly dose (mg/m^2) from all routes of administration. Bisphosphonate therapy was provided according to the local standard of care. Data were included only up to the point of bisphosphonate initiation.

Quantification of Glucocorticoid Exposure

The dose of systemic glucocorticoid (GC) therapy (oral and intravenous) received during the four-year observation period was converted to prednisone equivalents, expressed as mg/m^2 . GC exposure was described as five time-dependent variables up until the date of each VF assessment, as follows (24–26): (1) average daily dose, defined as the total amount of GC per body surface area divided by the total number of days in the observation period; (2)

duration of GC therapy, expressed as the number of days on GC since diagnosis; (3) GC dose intensity, defined as the total amount of GC per body surface area divided by the number of days receiving GC during the observation period; (4) recent average daily GC dose (i.e., average daily dose in the 12 months immediately preceding each spine radiograph); and (5) recent duration of GC (i.e., the number of days in receipt of GC in the 12 months preceding each annual spine radiograph).

Vertebral Fracture Assessment

VF were assessed at baseline and then annually from lateral thoracolumbar spine radiographs. Spine radiographs were scored independently by two pediatric radiologists (MAM and NS) using the modified Genant semi-quantitative method (27). A third radiologist (BL) resolved any discrepancies. The Genant methodology as applied to children with ALL has been described elsewhere (5, 6). An incident VF was defined as a new fracture in a previously normal vertebral body or worsening of an existing VF (i.e., an increase in the Genant grade by at least 1).

Lumbar Spine BMD, Bone Age and Second Metacarpal Morphometry

Within 30 days of GC initiation, areal lumbar spine (LS) BMD was measured in the anterior-posterior direction (L1–L4) by dual-energy x-ray absorptiometry using either Hologic (QDR 4500, three centers; Discovery, two centers; Delphi, one center) or Lunar systems (Prodigy, four centers) and repeated every six months thereafter. Machines were cross-calibrated as previously described. (5, 6). The raw LSBMD results were converted to Hologic units, and Z-scores were generated using the Hologic 12.3 normative database. Left hand and wrist radiographs were obtained at baseline and annually to determine bone age (28) and second metacarpal percent cortical area (5).

Statistical Analysis

Analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA). Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Box plots were used to describe the changes of average daily GC dosage, as well as LSBMD and BMI Z-scores over time. Mean differences were compared using paired or unpaired t-tests as appropriate.

The person-years incidence rate was calculated as the number of subjects with incident VF divided by the sum of the follow-up times for each subject at risk. The annual incidence proportions were calculated as the number of subjects with incident VF divided by the number of subjects who completed the VF assessment at the end of the specified time periods. To express the four-year cumulative VF incidence as a proportion, it was assumed that the children lost to follow-up or with missing data had the same probability of developing incident VF over four years as observed in the rest of the cohort.

Extended Cox's regression models, which allow non-proportional hazards, recurrent events and time-varying covariates (29), were used to determine the association between incident VF and (1) time-independent risk factors including age, sex, leukemia risk category, and

prevalent VF at baseline, and (2) time-dependent risk factors including bone age, pubertal stage, GC and methotrexate exposure, BMI and LSBMD Z-scores, second metacarpal percent cortical area Z-score, level of physical activity, back pain and average daily calcium and vitamin D intake. Prevalent VF at baseline were further grouped into three categories: absence of prevalent VF, mild VF (grade 1 as the maximum grade), and moderate/severe VF (grade 2 or more as the maximum grade). Data were censored either when the child reached the 48 month visit, at the last available follow-up visit or when bisphosphonate therapy was initiated, whichever occurred first. A test for non-proportional hazards using the Schoenfeld residuals (29) was performed, and smooth estimates of hazard ratios (HR) were calculated using the method of Therneau and Grambsch (29). If the proportional hazards assumption was not rejected at the 0.05 significance level, the constant HR was used to reduce the risk of overfitting bias (30). All multivariate models were adjusted for sex and height Z-scores (at either baseline or each subsequent VF assessment depending on which LSBMD Z-scores measurements were included in the models). Selection of risk factors for inclusion in the final models was guided by clinical judgment, with the effects from the extended Cox's models expressed as the HR, corresponding 95% confidence interval (CI) and the associated *p*-value.

Results

Clinical Characteristics of the Cohort

Of the 368 children approached for participation; 161 declined and 19 were excluded because of failure to undergo the baseline bone health evaluation within the specified time frame. Of the remaining 188, the number of children with a valid VF assessment at baseline, 12-, 24-, 36-, and 48-month follow-up visits were 186, 155, 147, 141, and 136 respectively. The reasons for lack of available data at each time point are presented in Figure 1. Demographic and clinical variables at baseline and clinical variables up until the last time-point for which there were available data did not differ significantly between those with and without complete annual assessments (data not shown).

Descriptions of this cohort at baseline and 12 months have been previously published (5, 6). In brief, the baseline profile of this cohort was as follows: median age, 5.3 years (IQR 3.4 to 9.7), 58% boys; 75% Caucasian, 90% with precursor B-cell ALL and 10% with T-cell ALL, 63% with standard risk and 37% with high risk ALL. Baseline VF assessments occurred at a median of 18 days from chemotherapy initiation (IQR range 7 – 25 days); the baseline prevalence of VF was 16% (5). Children were treated according to Children's Oncology Group (nine sites) or the Dana-Farber Cancer Institute (one site) protocols (Supplemental Table).

The Frequency and Pattern of Incident Vertebral Fractures

A total of 105 incident VF (76 thoracic and 29 lumbar) were identified in 38 children during the four years following diagnosis. The unadjusted VF incident rate was 8.7 per 100 person-years, with a four-year cumulative incidence of 26.4%. Eight children had incident VF at two time points, four had incident VF at three time points (i.e., a recurrence of incident VF), and the remaining 26 children had incident VF at a single time point. Of the 29 children with

VF at baseline, 65% had incident VF in the subsequent four years. The number of children with incident VF at each annual time point and the annual incidence proportions are presented in Table 1. Most of the VF burden occurred early in the patient's treatment course: 41 out of 50 children (82%) had their first VF identified at baseline or at 12 months, and 44 out of 50 children (88%) had their first VF within 24 months.

The anatomical distribution of incident VF, fracture morphology and severity are presented in Figure 2. Of the 105 incident VF, 85 (81%) were in previously normal vertebral bodies, whereas 20 (19%) were worsening of an existing fracture. Eighteen of 38 children (47%) had a single incident VF, nine children (24%) had two incident VF and 11 children (29%) had 3 or more incident VF. The maximum number of incident VF per child was 16 ($N = 1$). Nineteen children (50%) had mild VF as the worst grade, 13 (34%) had moderate VF, and 6 (16%) had severe VF. Overall, 61% of children with incident VF reported back pain in the preceding 12 months and 39% were asymptomatic. In those with moderate or severe incident VF, 65% reported back pain in the preceding 12 months compared to 39% of children with mild incident VF. Twelve out of 38 children (32%) on Dana Farber protocols developed incident VF over 4 years compared to 26/148 (18%) on Children's Oncology Group protocols.

Glucocorticoid Exposure, Disease Activity and Lumbar Spine BMD and Body Mass Index Z-score Trajectories

The average daily GC dose for the first 6 months was high (14.2 ± 5.2 mg/m² for boys and 12.4 ± 4.3 mg/m² for girls [mean $\pm$ SD]) and then decreased to 8.5 ± 5.4 mg/m² for boys and 8.5 ± 4.4 mg/m² for girls by 12 months. By 30 months, 90% of girls had completed chemotherapy and by 42 months, 96% percent of boys had completed therapy. Table 2 shows that GC exposure was significantly higher on Dana-Farber versus Children's Oncology Group protocols.

Baseline LSBMD Z-scores were low compared with healthy average (LSBMD Z-score $\pm$ of -1.2 ± 1.3 ; $p < 0.001$). Of the children with incident VF over 4 years, 63% had LSBMD Z-scores of < -2 and 95% had BMD Z-scores < -1.0 . The LSBMD Z-score increased overall following the baseline assessment (LSBMD Z-score -1.1 ± 1.1 at 1 year increasing to -0.7 ± 1.2 at 4 years). In contrast, the BMI Z-scores doubled in the first two years (BMI Z-scores of 0.57 ± 1.6 at baseline, increasing to 1.2 ± 1.1 at 2 years). The BMI Z-scores then declined to 0.8 ± 1.2 at 4 years. Descriptions of the GC dosing pattern, LSBMD and BMI Z-scores over the study period are presented in Figure 3.

Risk Factors for Incident Vertebral Fractures

Multivariate models showed that every 10 mg/m² increase in average daily GC dose was associated with a 5.9-fold increased VF risk (Model 1: HR = 5.9; 95% CI 3.0 – 11.8; $p < 0.01$, Table 3). In addition, every 10 mg/m² increase in recent (12 months preceding the annual VF assessment) average daily GC dose was associated with a 5.1-fold increased VF risk (Model 4: HR = 5.1; 95% CI, 2.8 – 9.5; $p < 0.01$). Furthermore, every 10 mg/m² increase in recent GC dose intensity was associated with a 20% increased VF risk (Model 5: HR = 1.2; 95% CI, 1.1 – 1.4; $p < 0.01$). In contrast, GC dose intensity and duration of GC

therapy were not significantly associated with an increased VF risk. All multivariate models showed that prevalent VF around the time of diagnosis (regardless of severity), younger age and lower LSBMD Z-scores at the time of each VF assessment (year 1 – 4 inclusive) were significantly associated with an increased VF risk. The following variables were excluded from our final, reported models given their lack of significance in the multivariate regression modeling: calcium and vitamin D intake, bone age, pubertal stage, sex, second metacarpal percent cortical area Z-score, recent back pain, and physical activity.

The LSBMD Z-score at diagnosis was highly correlated with prevalent VF at diagnosis and with the LSBMD Z-score at years 1 to 4, inclusive. Therefore, another multivariate model was generated based on model 1 in order to assess the association between incident VF and LSBMD Z-score at diagnosis, by removing prevalent VF at diagnosis and LSBMD Z-score at years 1 to 4. This model showed that every one SD reduction in LSBMD Z-score at baseline was associated with an 80% increased risk of incident VF in the ensuing 4 years (HR = 1.8; 95% CI, 1.5 – 2.3; $p < 0.01$). In this model, the average daily GC dose was significantly associated with an increased VF risk (HR = 4.8; 95% CI, 2.6 – 8.6; $p < 0.01$) while age became non-significant.

To explore the effect of puberty on VF risk, we first described the proportion of children with at least Tanner Stage 2 pubertal development among those with VF (20%) compared to those without VF (19.9%, $p = 0.982$). Next, we evaluated whether children with and without VF had a difference in bone age compared to chronological age at the annual study time points. There was no difference between bone age and chronological age at baseline, 12, 48, 60 and 72 months (data not shown). However, children both with VF ($p = 0.001$) and without VF ($p < 0.001$) had evidence of a delayed bone age relative to chronological age at 24 months (0.4 ± 0.7 years for both groups) and at 36 months (0.3 ± 0.7 for children with VF ($p = 0.031$); 0.2 ± 0.7 for children without VF ($p = 0.008$)). A univariate Cox's regression analysis with time to incident VF as the outcome and pubertal stage as the time-dependent risk factor showed no difference between those with Tanner Stage 2 to 5 versus Stage 1 puberty (HR = 0.69, 95% CI, 0.32 – 1.47, $p = 0.33$).

Discussion

There are a number of novel observations in this study with important implications for clinical care. First, we observed that VF are common (occurring in 26.4% of children over four years), with the highest annual incidence recorded in the first year of treatment. This is the same interval over which the children received the highest GC exposure. We demonstrated that the annual VF incidence declined steadily thereafter up to 48 months, with a concurrent decrease in GC exposure. Second, we show that prevalent VF of any severity around the time of diagnosis is a strong predictor of incident VF not only at 12 months (6) but also over the entire 4 years. Third, we report that incident VF are frequently asymptomatic and thereby go undetected in the absence of routine surveillance. Combined, these observations highlight important principles that can inform approaches to spine health monitoring in this setting.

Other national longitudinal studies have also reported the frequency of VF in children with ALL, though none as high as our report (31, 32). The lower incidence in other studies may at least partly reflect that VF were identified following only symptomatic presentation, whereas our standardized surveillance detected both symptomatic and asymptomatic VF. Hogler et al. (the United Kingdom) (31) described a retrospective, five-year incidence of 13.5% in pediatric ALL (which included all fracture types); 3.6% of children in this cohort had VF. In another study, te Winkel et al. (Netherlands) (32) reported a three-year all-fracture cumulative incidence of 17.8%; 2% of the children in this cohort had incident VF.

There are no other published studies which have assessed specific predictors of VF in the pediatric ALL setting. In addition to prevalent VF around the time of diagnosis, the strongest predictors of 4-year incident VF were total average daily GC dose, recent average daily GC exposure, and recent GC dose intensity. That GC exposure is a clinical predictor of incident VF is not surprising given the potent osteotoxic effects of GC on bone cellular metabolism (33) Rayar et al. (Dana Farber 1995 to 1996 protocols) (34) showed that dexamethasone was associated with a higher risk of fractures (all types) compared to prednisone. In our cohort, almost all of the children (95%) received dexamethasone as part of their chemotherapy, 44% of whom had also received prednisone; only 1% of children were treated with prednisone alone. The fact that almost all of the children had been treated with dexamethasone precluded our ability to tease out the relative contribution of dexamethasone versus prednisone to VF risk.

The use of dual energy x-ray absorptiometry for BMD quantification has posed challenges in pediatric bone health care due to uncertainties as to its role in diagnosis and monitoring of osteoporosis in children. This has been due in large part to a lack of information on the relationship between BMD Z-scores and fractures in children with underlying illnesses. Here we provide concrete evidence that lower spine BMD Z-scores at baseline and at the time of each annual VF assessment predict an increased VF risk. We did not find a significant relationship between declines in spine BMD Z-scores and incident VF (between baseline and six months, or between any other interval in the four-year period). This observation is similar to the study of children with ALL by te Winkel et al. (32) who found that children with incident fractures (all types) had lower spine BMD Z-scores at diagnosis and during treatment compared to those without, but no differences in BMD Z-score changes over time. These findings contrast reports in adults (33) and in children with rheumatic disorders (35). This may reflect the fact that while LSBMD Z-scores are low in pediatric ALL, overall there is a drive to recovery (32, 36–38). Since leukemia typically reaches a very low minimal residual disease state rapidly with treatment, any leukemia-derived cytokine effect on skeletal metabolism is expected to be short-lived. The manner of therapy (with short GC pulses that define ALL maintenance therapy) may also play a role in these differences.

We have previously shown that the use of a BMD Z-score cut-off to diagnose a child with osteoporosis is not a valid approach, in part given the observation (as shown here) that children with VF frequently have BMD Z-scores > -2 and even > -1 SD (39); on the other hand, using the BMD Z-score as a continuous variable in the context of research studies

remains a valid approach to identify the relative contribution of different predictors to a given clinical outcome.

Overall, we observed that 39% of children with incident VF did not report symptoms; we further observed that just over one third of those with even moderate and severe collapse were asymptomatic. Therefore, it is not surprising that back pain was not a significant predictor of incident VF. The long term clinical impact of asymptomatic VF merits further study. That young age was a predictor of incident VF (albeit weak compared to prevalent VF at baseline and GC exposure) is consistent with other reports (31, 32). Possible explanations for the observed relationship between younger age and incident VF include increased sensitivity to GC effects on bone, or that older age may be protective against the toxic effects of GC therapy because of higher bone turnover or larger skeletal dimensions.

Interestingly, calcium and vitamin D intake and physical activity were not related to VF, consistent with other prospective, pediatric chronic illness reports (6, 35, 40). Quantification of nutrient intake and physical activity by questionnaire is less precise than direct measurements such as serum biomarkers of nutrition or physical fitness outcomes; our methods may not have been sufficiently sensitive to reveal associations. We also explored whether puberty had a protective effect on VF risk, particularly since younger children were at increased risk for VF. We were unable to show an independent effect of puberty on VF risk; however, mild delay in skeletal maturation at 24 and 36 months may have impacted these analyses. Overall, insufficient power may have led to failure to detect additional predictors of bone strength; as such, larger cohorts may be needed to understand the role of nutrient intake, puberty and physical activity alongside proven predictors including GC exposure and prevalent VF.

In summary, we have shown the proportion of children with incident VF in the four years following ALL diagnosis is 26.4%, that most of the incident VF burden is in the first year (when GC exposure is highest), and that discrete clinical predictors are evident around the time of diagnosis (VF at diagnosis, low LSBMD Z-scores and younger age) and during chemotherapy (GC exposure and low LSBMD Z-scores). These natural history observations provide important data to support further study of the impact of including a spine radiograph as part of the routine bone health assessment in at-risk children with ALL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALL	acute lymphoblastic leukemia
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
GC	glucocorticoid
HR	hazard ratio
IQR	interquartile range
LS	lumbar spine
SD	standard deviation
VF	vertebral fracture

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Appendix

The Canadian STOPP Consortium (a Pan-Canadian, Pediatric Bone Health Working Group):

*Executive Committee Member; §Publications and Presentations Committee Member

Principle Investigator: Leanne M. Ward*§

Co-ordinating Center: Children's Hospital of Eastern Ontario, Ottawa, Ontario: Leanne M. Ward*§ (Study Principal Investigator), Janusz Feber*§ (Nephrology), Jacqueline Halton*§ (Oncology), Roman Jurencak (Rheumatology), MaryAnn Matzinger (Radiology, Central Radiograph Analyses), Johannes Roth (Rheumatology), Nazih Shenouda§ (Radiology, Central Radiograph Analyses), Jinhui Ma (Research Methods and Statistics). Ottawa Hospital Research Institute, Ottawa Methods Centre Ottawa, Ontario: David Moher*§ (Research Methods), Karen Watanabe-Duffy (Rheumatology), Monica Taljaard (Research Methods and Statistics)

Participating Centers: Alberta Children's Hospital, Calgary, Alberta: Josephine Ho (Site Principal Investigator, from July 2013 to current), David Stephure (Bone Health, Site Principal investigator until July, 2013), Reinhard Kloiber (Radiology), Victor Lewis (Oncology), Julian Midgley (Nephrology), Paivi Miettinen (Rheumatology); British Columbia Children's Hospital, Vancouver, British Columbia: David Cabral* (Site Principal Investigator), David B. Dix (Oncology), Tom Blydt-Hansen (Nephrology, from 2014), Kristin Houghton (Rheumatology), Helen R. Nadel (Radiology); British Columbia Women's Health Sciences Centre, and Dept. of Radiology, University of British Columbia, Vancouver, British Columbia: Brian C. Lentle§ (Radiology); Brock University, Faculty of Applied Health Sciences, St. Catharines, Ontario: John Hay§ (Physical Activity Measurements); Children's Hospital, London Health Sciences Centre, University of Western Ontario, London, Ontario: Robert Stein (Site Principal Investigator), Elizabeth Cairney (Oncology), Cheril Clarson (Bone Health), Guido Filler (Nephrology)§, Joanne Grimmer (Nephrology), Scott McKillop (Radiology, from 2012 to current), Keith Sparrow (Radiology, until 2012); IWK Health Center, Halifax, Nova Scotia: Elizabeth Cummings (Site Principal Investigator), Conrad Fernandez (Oncology), Adam M. Huber§ (Rheumatology), Bianca Lang*§ (Rheumatology), Kathy O'Brien (Radiology); McMaster Children's Hospital, Hamilton, Ontario: Stephanie Atkinson*§ (Site Principal Investigator), Steve Arora (Nephrology), Ronald Barr§ (Oncology), Craig Coblenz (Radiology), Peter B. Dent (Rheumatology), Maggie Larche (Rheumatology); Montréal Children's Hospital, Montréal, Québec: Anne Marie Sbrocchi (Site Principal Investigator, from 2013 to current), Celia Rodd§ (Site Principal Investigator, until 2013), Sharon Abish (Oncology), Lorraine Bell (Nephrology), Claire LeBlanc (Rheumatology), Rosie Scuccimarri (Rheumatology); Shriners Hospital for

Children, Montréal, Québec: Frank Rauch*[§] (Co-Chair, Publications and Presentations Committee and Ancillary Studies Committee); Ste. Justine Hospital, Montréal, Québec: Nathalie Alos* (Site Principal Investigator), Josée Dubois (Radiology), Caroline Laverdière (Oncology), Véronique Phan (Nephrology), Claire Saint-Cyr (Rheumatology); Stollery Children's Hospital, Edmonton, Alberta: Robert Couch* (Site Principal Investigator), Janet Ellsworth (Rheumatology), Maury Pinsk (Nephrology), Jacob Jaremko and Kerry Siminoski[§] (Radiology), Beverly Wilson (Oncology); Toronto Hospital for Sick Children, Toronto, Ontario: Ronald Grant* (Site Principal Investigator), Martin Charron (Radiology, until 2013), Diane Hebert (Nephrology); Université de Sherbrooke, Department of family medicine, Sherbrooke, Québec: Isabelle Gaboury*[§] (Biostatistics); Winnipeg Children's Hospital, Winnipeg, Manitoba: Shayne Taback[§] (Site Principal Investigator), Tom Blydt-Hansen (Nephrology, until 2014), Sara Israels (Oncology), Kiem Oen (Rheumatology), Martin Reed (Radiology), Celia Rodd[§] (Bone Health, from 2013 to current).

48 months, and *1 child returned subsequent to 48 months. At 36 months, among the 9 children who had a poor-quality spine radiograph (n=1) or did not undergo the spine radiograph (n=8), 7 children returned for a radiograph at 48 months, and *2 returned subsequent to 48 months. At 48 months, *9 children who had a poor-quality spine radiograph (n=3) or did not undergo the spine radiograph (n=6) at 48 months returned for a radiograph subsequent to 48 months. *For these children, their data beyond 48 months are not reported since this study focuses on the natural history in the first 4 years following diagnosis.

Figure 2.

A, Severity, frequency and distribution of incident vertebral fractures in children with ALL.

B, Distribution and frequency of incident VF morphology.

Figure 3.

Changes in mean glucocorticoid exposure, lumbar spine bone mineral density Z-scores and body mass index Z-scores over 48 months in children with leukemia.

Table 1

The baseline prevalence and annual incidence of vertebral fractures in the four years following leukemia diagnosis

Time Point (n)	Number of Patients with Prevalent VF and/or with a First Incident VF	Number of Patients with a Second Incident VF	Number of Patients with a Third Incident VF	Total Number of Patients with Prevalent or Incident VF	Total Number of Prevalent or Incident VF Events	Baseline Prevalence and Annual Incidence Proportion of VF, % (95% CI)*
Baseline (186)	29	NA	NA	29	75	15.6 (11.1 – 21.5)
12 months [‡] (155)	25	NA	NA	25	61	16.1 (11.2 – 22.7)
24 months [‡] (147)	7	7	NA	14	21	9.5 (5.8 – 15.4)
36 months (141)	4	3	4	11	18	7.8 (4.4 – 13.4)
48 months (136)	2	2	0	4	5	2.9 (1.1 – 7.3)

* Based on percent of subjects with an available spine radiographs at each time point

[‡] 13 children with their first incident VF at 12 months also had prevalent VF at baseline; similarly, 4 children with their first incident VF at 24 months also had prevalent VF at baseline.

Table 2

Comparison of glucocorticoid exposure for Dana-Farber versus Children’s Oncology Group protocols across different leukemia risk categories

GC exposure at 48 months' follow-up	Dana-Farber Cancer Institute			Children's Oncology Group			P for Comparison of the two protocols
	High risk (n=11)	Standard risk (n=15)	Overall (n=26)	High risk (n=33)	Standard risk (n=76)	Overall (n=109)	
Average daily GC (mg/m ²)	6.5 (0.8)	5.8 (1.6)	6.1 (1.3)	4.8 (1.1)	5.2 (1.5)	5.1 (1.4)	0.002
Cumulative GC (mg/m ²)	9,693 (1080)	8,748 (2507)	9,148 (2052)	7,307 (1571)	7,959 (2208)	7,776 (2018)	0.003

Data are means (SD)

Table 3
Multivariate Cox's regression models assessing the association between potential risk factors and incident vertebral fracture

Clinical parameter	Model 1: Average Daily GC Dose (10 mg/m ²)			Model 2: Average GC Dose-Intensity (10 mg/m ²)			Model 3: Duration of GC Therapy (years)			Model 4: Recent [#] Average Daily GC Dose (10 mg/m ²)			Model 5: Recent [#] GC Dose Intensity (10 mg/m ²)			Model 6: Recent [#] Duration of GC Therapy (month)		
	HR (95% CI)	p		HR (95% CI)	p		HR (95% CI)	p		HR (95% CI)	p		HR (95% CI)	p		HR (95% CI)	p	
↑ GC exposure	5.9 (3.0 – 11.8)	<0.01		1.1 (0.9 – 1.3)	0.29		0.3 (0.1 – 1.8)	0.18		5.1 (2.8 – 9.5)	<0.01		1.2 (1.1 – 1.4)	<0.01		1.11 (0.9 – 1.3)	0.18	
Prevalent VF, mild vs none	4.2 (1.9 – 9.6)	<0.01		4.3 (2.1 – 8.9)	<0.01		4.3 (2.1 – 8.8)	<0.01		4.6 (2.2 – 9.8)	<0.01		1.6 (2.3 – 9.5)	<0.01		4.1 (2.0 – 8.5)	<0.01	
Prevalent VF, moderate/severe vs none	6.2 (3.4 – 11.4)	<0.01		6.3 (3.5 – 11.1)	<0.01		6.6 (3.7 – 11.8)	<0.01		6.1 (3.4 – 11.2)	<0.01		6.2 (3.4 – 11.3)	<0.01		5.8 (3.2 – 10.5)	<0.01	
↓LSBMD Z-score, at the time of VF assessment	1.6 (1.2 – 2.2)	<0.01		1.5 (1.1 – 2.0)	0.03		1.4 (1.0 – 2.0)	0.03		1.5 (1.1 – 2.0)	0.01		1.4 (1.0 – 1.9)	0.04		1.5 (1.1 – 2.0)	0.02	
↓ Age (years)	1.1 (1.0 – 1.2)	0.02		1.1 (1.0 – 1.2)	0.04		1.1 (1.0 – 1.2)	0.04		1.1 (1.0 – 1.2)	0.05		1.1 (1.0 – 1.2)	0.06		1.1 (1.0 – 1.2)	0.07	

All models adjusted for sex and height Z-scores at the time of VF assessment

[#]Recent: 12 months preceding the vertebral fracture assessment