SHORT COMMUNICATION

Changes in Bone Mineral Density During Therapy in Childhood Acute Lymphoblastic Leukemia

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Quantitative computed tomography was performed to determine bone mineral density (BMD) at initial presentation and following 6-months of therapy in children with acute lymphoblastic leukemia (ALL). Of 46 children enrolled, the complete set of observations was available in 32. The combined mean BMD of three lumbar vertebrae at diagnosis and during treatment were 167.1±27.4 and 148.8±31.4 mg/cm^3, respectively (*P*=0.001). Twenty six children (81.2%) had a decrease in BMD on treatment. The mean BMD for each of 3 vertebrae declined as well. The mean T-scores at diagnosis and during therapy were –0.15±0.9 and –0.86±1.0, respectively (*P*=0.001). Conventional radiographs revealed metaphyseal lucencies which were replaced with metaphyseal dense bands with therapy. To conclude, there was a significant reduction of BMD in children with ALL following 6-months of treatment.

Keywords: *Acute lymphoblastic leukemia, Bone mineral density, Quantitative computed tomography.*

Bone morbidity is a significant long-term complication of successful treatment of acute lymphoblastic leukemia (ALL)(1). The study was designed to prospectively determine bone mineral density (BMD) and radiological changes in children with ALL at initial presentation, and following 6-months of therapy.

METHODS

Consecutive cases of ALL were enrolled from July to December 2004, and followed up for next 6 months. Children who had received ≥7 days of chemotherapy prior to referral, or those with relapsed disease were excluded. UKALL-X protocol was administered with following modifications: 3-drug induction with vincristine, prednisone and L-asparaginase; 6-weekly pulses of vincristine/dexamethasone instead of 4, and intensification delayed by 1-week to ensure count recovery.

Quantitative computed tomography (QCT) for assessment of BMD was performed at diagnosis and following 6 months of therapy. The measurement was done on QCT-5000 bone densitometry system (General Electric, Columbia, KY-USA), which allows highly automated vertebral BMD measurements. Mineral content was determined in the midplane of three lumbar vertebrae (L1 to L3), in a single 10-mm slice, obtained at each level. BMD was expressed in units of population standard deviation; the T-score = ± number of SDs from young mean. Z-scores were estimated as well. The T and Z-scores(2) obtained at 6 months were compared with respective scores at diagnosis. *X*-ray lateral-view dorsolumbar spine and antero-posterior view of bilateral knee joints was performed at presentation and following 6 months of therapy.

The study was approved by institutional ethics board and consent was obtained from parents.

RESULTS

Out of 46 cases of ALL enrolled prospectively, 11 were lost to follow-up and 3 died during induction. Of 32 children (mean age, 5.5±3.0 years) who completed the study, 28 were boys. A history of bone pains was elicited in 9 (28.3%). No child had a fracture during the study period. The mean WBC count at diagnosis was 34,835±53,359/μL (range:800-2,00,000μL).

Following 6 months of therapy, 26 children (81.2%) had a decrease in BMD. The BMD increased in the remaining 6. Seven children (21.8%) had T-scores in osteopenic or osteoporotic range at diagnosis as compared to 17(53.1%) during therapy (*P*=0.01) (**Table I**). The BMD declined comparably in children younger and older than 5 years after treatment. There was a significant decline in all BMD measurements in children with WBC count <50,000/μL. Children with counts ≥50,000/μL had a significant decline in BMD of L3 vertebra. Other BMD values demonstrated an insignificant fall. BMD for each vertebra, as well as the mean BMD of 3 vertebrae had a significant decrease during therapy for boys. The T and Z-scores had a statistically significant decline as well. All BMD values increased significantly in girls.

Four children (12.5%) had a normal knee joint radiograph at diagnosis, compared to 1(3.1%) after 6 months. Metaphyseal lucencies were observed in 11(34.3%) patients initially, and in 1(3.1%) during therapy (P=0.002). Dense metaphyseal bands were seen in 24 (75%) patients during treatment as compared to 2 (6.3%) at diagnosis (*P*<0.001). Eight (25%) patients had a normal dorsolumbar spine *X*-ray at diagnosis, as compared to 5 (15.6%) after 6 months. Severe osteopenia of spine was observed initially in 6 (18.7%) patients; the number increased to 13 (40.6%) after 6-months (*P*=0.055). Lucency and osteopenia of the ankle joint and lytic lesions of tibia were observed in one patient each.

TABLE I CHANGES IN BONE MINERAL DENSITY (BMD) WITH THERAPY

	At diagnosis	After 6 months	*P* value
BMD at L1			
mean±SD	171.0±29.6	152.67±29.89	0.001
range	112.6–243.8	107.5–209.4	
median	170.9	150.5	
BMD at L2			
mean±SD	167.0±27.7	149.6±34.0	0.001
range	114.1–231.9	85.2–213.2	
median	169.3	148.3	
BMD at L3			
mean±SD	164.0±29.0	145.0±33.9	0.003
range	107.8–221.0	77.2–215.0	
median	167.7	143.7	
Mean BMD (L1, L2 and L3)			
mean±SD	167.1±27.4	148.8±31.4	0.001
range	116.0–232.0	95.8–203.0	
median	170.9	146.6	
T-score			
mean±SD	–0.15±0.9	–0.86±1.0	0.001
range	–2.0 to +2.1	–2.6 to +1.5	
median	–0.05	–1.0	
Z-score			
mean±SD	–0.43±1.2	–1.18±1.1	0.0002
range	–2.3 to +3.9	–3.1 to +1.4	
median	–0.5	–1.3	

**BMD is measured in mg/cm^3; L1: first lumbar vertebra, L2: second lumbar vertebra, L3: third lumbar vertebra*

DISCUSSION

Majority of BMD studies have been performed using dual-energy *X*-ray absorptiometry (DXA)(3,4). However, DXA has several drawbacks in children(2). It measures areal BMD and provides no information on bone architecture, whereas QCT describes volumetric BMD, measures bone dimensions and distinguishes between cortical and trabecular bone. It permits an unambiguous distinction between the effects on bone size and density(5).Therefore, we chose to measure BMD with QCT. A disadvantage is the relatively higher radiation dose with QCT.

We observed a significant reduction in the BMD following 6-months of therapy. Osteopenia as well as osteoporosis, defined by T-scores, were found in significantly more patients during treatment. The BMD for each vertebra, as well as the mean BMD of

WHAT THIS STUDY ADDS?

- Bone mineral density measured by QCT, is significantly reduced following six months of therapy in Indian children with acute lymphoblastic leukemia.

all 3 vertebrae was reduced significantly. The T and Z-scores had significant reduction as well. Our results are similar to several earlier studies(6-8). Hoorweg, *et al*.(9) have reported BMD to be significantly lower in long-term survivors of ALL in contrast to Mandel, *et al*.(10).

Chemotherapy, cranial irradiation and reduced physical activity are implicated in reduction of BMD(11). Lumbar spine is predominantly trabecular which is more sensitive to effects of chemotherapy(12). Bone loss induced by corticosteroids has been shown to be most rapid in lumbar spine. The damaging effect of irradiation is one consistent factor in the aforementioned studies and is attributed to hypothalamic-pituitary axis dysfunction, leading to growth hormone deficiency. Mean cumulative dose of prednisone, dexamethasone and oral methotrexate that our patients received during first 6 months of treatment were 1300, 90 and 240 mg/m^2, respectively.

Although mean BMD of the study cohort declined significantly, the absolute BMD of spine was increased in 6 (18.7%). Arikoski, *et al.*(12) found increased lumbar BMD in 11/26 patients.This observation in few patients is intriguing. In our study, a significant decrease was seen in BMD for boys. Studies have reported BMD to be lower in male survivors of ALL(1,13). This is attributed to decreased androgenic function due to malignancy induced gonadal damage(1).The cause of increased BMD in girls is uncertain. A decrease in BMD was observed irrespective of age in index study. Arikoski, *et al*.(12) reported bone loss to be more pronounced in younger patients while Barr, *et al*.(14) found osteopenia to correlate with older age.

Halton, *et al*.(8) reported skeletal abnormalities in 21/40 patients on plain radiology(8). Initial osteopenia and lucency are attributed to leukemic infiltration while the subsequent reduction in bone mineral content is attributed to chemotherapy(8). Dense metaphyseal bands during therapy might be due to healing of leukemic lucencies and enhanced mineralization, similar to callus formation observed following fractures(12).

To conclude, a significant reduction in BMD was observed in children with ALL following 6 months of therapy. However, there is a need to have normative data of BMD in children. The challenge is to make the assessment of risk of osteoporosis an integral part of management of ALL, so that therapy can be initiated prior to occurrence of bone morbidity.

Contributors: AK enrolled the cases and prepared the draft. DB supervised the study and critically evaluated the manuscript. NK reported the radiology. RKM and AT conceived and guided the study. RKM will act as the guarantor.

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