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Early injury to cortical and cancellous bone from induction chemotherapy for adolescents and young adults treated for acute lymphoblastic leukemia☆

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ABSTRACT

Diminished bone density and skeletal fractures are common morbidities during and following therapy for acute lymphoblastic leukemia (ALL). While cumulative doses of osteotoxic chemotherapy for ALL have been reported to adversely impact bone density, the timing of onset of this effect as well as other changes to bone structure is not well characterized. We therefore conducted a prospective cohort study in pre-adolescent and adolescent patients (10–21 years) newly diagnosed with ALL ($n = 38$) to explore leukemia-related changes to bone at diagnosis and the subsequent impact of the first phase of chemotherapy ("Induction"). Using quantitative computerized tomography (QCT), we found that pre-chemotherapy bone properties were similar to age- and sex-matched controls. Subsequently over the one month Induction period, however, cancellous volumetric bone mineral density (vBMD) decreased markedly (-26.8%, $p < 0.001$) with sparing of cortical vBMD (tibia -0.0%, $p = 0.860$, femur -0.7%, $p = 0.290$). The tibia underwent significant cortical thinning (average cortical thickness -1.2%, $p < 0.001$; cortical area -0.4%, $p = 0.014$), while the femur was less affected. Areal BMD (aBMD) concurrently measured by dual-energy X-ray absorptiometry (DXA) underestimated changes from baseline as compared to vBMD. Biochemical evidence revealed prevalent Vitamin D insufficiency and a net resorptive state at start and end of Induction. Our findings demonstrate for the first time that significant alterations to cancellous and cortical bone develop during the first month of treatment, far earlier during ALL therapy than previously considered. Given that osteotoxic chemotherapy is integral to curative regimens for ALL, these results provide reason to re-evaluate traditional approaches toward chemotherapy-associated bone toxicity and highlight the urgent need for investigation into interventions to mitigate this common adverse effect.

☆ These results have not been previously presented

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1. Introduction

Chemotherapy for pediatric acute lymphoblastic leukemia (ALL) is known to adversely impact bone density and is associated with skeletal fractures [1–4]. Recent reports have described the onset of osteotoxicity earlier than previously thought with bone changes now understood to primarily occur during active therapy [5,6] with potential improvement for some in the years following therapy [7,8]. While the etiology for the adverse influence of ALL therapy on bone is likely multi-factorial, a significant contributor is prolonged and repetitive high-dose glucocorticoid steroids given throughout the two to three years of ALL treatment [9]. Prior studies of osteotoxicity have therefore principally focused on the cumulative effects of ALL treatment on bone density after months or even years of ALL therapy [10–14]. Yet, ALL therapy commonly begins with a treatment phase (Induction) that relies on an established backbone of glucocorticoid steroids to obtain the crucial initial remission. Recently, the large Canadian "STeroid-associated Osteoporosis in the Pediatric Population (STOPP)" clinical trial revealed that occult fractures and vertebral compression are already frequent occurrences even during this first treatment phase. However, many studies that have examined bone during this early time period, including the STOPP trial [15] and others [13,16], have grouped much, or all, of Induction chemotherapy into a single cross-sectional time-point, thereby precluding examination of changes to bone during Induction itself from the days or weeks of osteotoxic chemotherapy [16].

In the present study, we sought to address this knowledge gap through focusing specifically on changes to bone during the Induction phase and to gain greater insight into potential changes due to leukemia infiltration of the marrow even prior to therapy. Use of the advanced imaging modality of quantitative computerized tomography (QCT) provided the opportunity to gain detailed information on bone properties, such as three-dimensional volumetric BMD (vBMD), bone geometry, and other contributors to bone strength. As much of the existing bone density literature in ALL uses the well-validated, and more commonly available, dual-energy x-ray absorptiometry (DXA) to assess areal BMD (aBMD) [12,17,18], we concurrently assessed whole body aBMD in our cohort with DXA as well. To our knowledge, this is the first study to use QCT to determine detailed bone structure and density at the time of diagnosis and to focus on early changes from Induction therapy for childhood ALL.

2. Materials and methods

2.1. Study population

Pre-adolescents, adolescents and young adults (AYA) at least ten and less than 21 years of age newly diagnosed with National Cancer Institute/Rome High-Risk B-Precursor (HR BP-ALL) or T-cell ALL were enrolled in a prospective study of osteotoxicity within 24 h from the initiation of Induction chemotherapy. An AYA population was selected for study as an at-risk target population with greater rates of chemotherapy-induced osteotoxicity [19,20]. All patients were treated following Children's Oncology Group (COG) protocols (AALL0232, AALL1131, AALL0434) and uniformly received a 28 day Induction regimen using vincristine, pegylated L-asparaginase, anthracycline (daunorubicin or doxorubicin), and a glucocorticoid (either prednisone 60 mg/m^2/day for 28 days or dexamethasone 10 mg/m^2/day for 14 days). Due to toxicity from the treatment intensity of Induction chemotherapy, not all subjects were able to complete all imaging and assessments (Supplemental Fig. 1, Consort diagram). Demographic and treatment information included age, sex, ethnicity, Body Mass Index percentile (BMI%), leukemia phenotype, treatment regimen, and cumulative steroid dose delivered. For evaluation of bone density, geometry, and estimated biomechanical resistance to force at the time of diagnosis (i.e. due to onset of the leukemia), bone density, geometry, and structural properties in the treatment group were compared to healthy children recruited separately at our institution for prospective studies of bone. The individual cohorts for vertebral and tibia comparisons were drawn from two separate studies of children free of chronic disease, not on steroids or medications affecting growth and development, and without metal implants precluding imaging. Matched controls were selected from these healthy cohorts based on age (+/− 0.1 years) and sex for comparison of bone measures and body composition. No control group for femur comparison was available. The clinical trial was approved by the Institutional Review Board and federally registered (NCT01317940). Informed consent was obtained for all subjects.

2.2. Imaging protocols

Subjects underwent imaging within 96 h from start of chemotherapy and again 28–35 days later at the end of the Induction phase and prior to any subsequent chemotherapy. Subjects were imaged using QCT; to reduce operator-induced intra-patient (for serial imaging) and inter-patient variability in radiographic assessment, all imaging was performed primarily by the same certified radiology technician. The lumbar spine was assessed in all participants using a scan of the L1–L3 vertebrae, and femurs and tibias were assessed at the mid-shaft. For the spine, the site to be scanned was identified with a lateral scout view, and a single 10-mm axial slice was obtained at the mid-portion of each of the three vertebral bodies—L1, L2, and L3. For the femur, the site to be scanned was identified visually as the midpoint between the most distal and central aspect of the patella and the greater trochanter, and a single 10 mm slice was obtained at the femoral mid-shaft. For the tibia, contiguous 1-mm slices were obtained covering the entire tibia. One slice halfway between the tibial plateau and the most distal point of the medial malleolus was then selected for analysis. All femur and spine scans were performed on the same scanner (General Electric LightSpeed QX/I, Milwaukee, WI) using the same mineral reference phantom for simultaneous calibration (CT-T bone densitometry package; General Electric). All tibia scans were completed using a different scanner (Philips Gemini GXL, Philips Medical Systems Inc., Cleveland, OH) and mineral reference phantom (Mindways Model 3 CT Calibration Phantom, Philips Gemini GXL, Philips Medical Systems Inc., Cleveland, OH).

Image analysis for the femur and tibia was done using custom algorithms in Matlab version R2013b (Mathworks, Natick, MA). For the diaphysis, geometric properties were calculated using contours from edge detection based on the density gradient between neighboring voxels and included average cortical bone density, total bone area, cortical bone area, medullary canal area, average cortical bone thickness, maximum principal (Imax), minimum (Imin) principal, and polar (J) moments of inertia, and average marrow density. Of note, the site was changed from tibia to femur midway through the study due to logistical changes at our institution; nonetheless, this adjustment provided the ability for us to compare change in cortical bone at two lower extremity sites.

For aBMD, a fan beam DXA densitometer (Delphi W; Hologic, Inc., Waltham, MA) in array mode was used and analyzed with the manufacturer's software. The coefficients of variation for measurements of fat, lean mass, and bone mineral content (BMC) are between 1.2 and 5% [21]. Since the primary comparison to a healthy cohort was established with QCT, to limit radiation exposure only whole-body DXA was performed to compare changes in BMD by the two modalities. Percent change from baseline during Induction for aBMD was calculated from whole body DXA for "Total body less head" (TBLH) and for the spine (total, thoracic, lumbar) from BMC divided by bone area.