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Original Article

Changes in Bone Health During the First Year of Cancer Treatment in Children

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Abstract

This study aimed to evaluate longitudinal changes in bone mineral density (BMD) and bone mineral content (BMC) in children with cancer during the first year of treatment. Thirty pediatric cancer patients (median age 11.2 [range 3.8–17.4] yr; 21 boys, 9 girls; 19 hematologic malignancies, 11 solid tumors) and 30 healthy controls were enrolled. Dual energy X-ray absorptiometry was performed at baseline and at 1, 6, and 12 mo for each pediatric cancer patient. There were no significant differences in age, sex, body weight, height, body mass index, serum vitamin D levels, BMD, and BMC among children with hematologic malignancies, those with solid tumors, and the controls at baseline. When the medians of BMD *Z*-scores were compared between different time intervals, whole-body BMD *Z*-score significantly decreased during the first year of cancer treatment ($p = 0.001$) in children with hematologic malignancies, especially during the first month ($p = 0.002$), and between 1 and 6 mo ($p = 0.006$). In children with solid tumors, whole-body BMD *Z*-score changed significantly only between 6 and 12 mo after treatment ($p = 0.043$). Generalized estimation equations for the analysis of trends in the whole-body BMD *Z*-scores revealed that there were significant downward trends between BMD *Z*-scores at baseline and those at 12 mo in children with hematologic malignancies and those with solid tumors. Cancer treatment significantly affects the bone health status at least during the first year, causing a significant decrease in BMD, especially during the first 6 mo for patients with hematologic malignancies and during the last 6 mo for those with solid tumors. Better strategies for treating changes in BMD based on the underlying cancer are necessary during cancer treatment in children.

Key Words: Bone mineral density; cancer treatment; children.

Introduction

Survival rates in pediatric cancer patients have continuously increased, up to 80%, within the last few decades owing to improvements in diagnostic methods and the evolution of chemotherapeutic protocols *(1,2)*. With substantial growth in the number of long-term childhood cancer survivors (CCSs), it is now estimated that 1 of every 640 young adults in the United States is a CCS *(3)*.

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Long-term CCSs are at risk of chronic health conditions resulting from cancer and its treatment *(1,3)*. These include secondary malignant neoplasms, cardiopulmonary toxicity, renal dysfunction, endocrine abnormalities, neuropsychiatric problems, and musculoskeletal abnormalities *(4,5)*. Among these problems, skeletal morbidity remains one of the most important problems for CCSs but is often overlooked despite the fact that impaired bone health can lead to fractures during and after cancer treatment *(6–8)*.

Acquisition of optimal peak bone mass and strength during childhood and adolescence is critical for the prevention of osteoporosis later in life *(9,10)*. Bone mass increases throughout childhood and adolescence, with peak bone mass achieved between 20 and 30 yr of age *(11,12)*. In children and adolescents diagnosed with cancer,

acquisition of peak bone mass may be adversely affected by cancer treatment, nutritional deficiencies, and reduced physical activity *(13,14)*. Thus, it is important to monitor bone health in these patients and to implement strategies to minimize the risk of developing osteoporosis and fragility fractures during and after cancer treatment.

To date, most studies on bone health in pediatric cancers have been cross-sectional, examining CCSs with a focus on hematologic malignancies, including acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma *(8,15–17)*. Therefore, little is known about the onset and development of bone loss during cancer treatment. The present study aimed to prospectively evaluate longitudinal changes in bone mineral density (BMD) and bone mineral content (BMC) in children with newly diagnosed cancer during the first year of treatment.

Patients and Methods

Study Subjects

Children with newly diagnosed cancer who received treatment with chemotherapy at the Seoul National University Bundang Hospital between April 2012 and October 2014 were recruited to participate in this prospective, longitudinal assessment of BMD and BMC. Thirty pediatric cancer patients (median age 11.2 [range 3.8–17.4] yr; 21 boys, 9 girls; 19 hematologic malignancies, 11 solid tumors) and 30 healthy controls were enrolled. Of the 19 hematologic malignancies, there were 8 cases of ALL, 4 cases of acute myelogenous leukemia (AML), 6 cases of lymphoma, and 1 case of Langerhans cell histiocytosis (LCH). The 11 solid tumors included 3 osteosarcomas, 2 brain tumors, 1 neuroblastoma, 1 Wilms tumor, 1 rhabdomyosarcoma, 1 Ewing sarcoma, 1 mesenchymal chondrosarcoma, and 1 solid pseudopapillary tumor of the pancreas.

The patients were treated according to pediatric cancer protocols consisting of multiple chemotherapeutic agents for 6–12 mo before the last follow-up measurement (Supplemental Table S1). ALL, lymphoma, and LCH patients received 40–60 mg/m^2 of prednisolone daily for 4–6 wk of the induction period. The total cumulative dose of corticosteroid was 1.2–5.9 g/m^2 during 6–12 mo of treatment. Methotrexate (48.0–84.0 g/m^2) and ifosfamide (9.0–63 g/m^2) were administered in solid tumor cases, including osteosarcoma patients. Busulfan- or melphalan-based conditioning regimens without total body irradiation were used for allogeneic or autologous hematopoietic stem cell transplantation (HSCT).

Relapsed cancer patients were excluded to eliminate the confounding effect of previous chemotherapy. Age- and sex-matched healthy controls, without any organic diseases, were enrolled from the pediatric outpatient clinic. Body weight was determined to the nearest 0.1 kg using a calibrated digital scale, and height was measured to the nearest 0.1 cm on a standard height board. Body mass index (BMI) was calculated as weight (kilogram) divided by height squared (square meter).

BMD and BMC Measurements

Factors related to bone health status, such as BMD and BMC, and body composition components as measured by dual-energy X-ray absorptiometry (DXA) were compared among the children with hematologic malignancies, children with solid tumors, and the controls at baseline. BMD (gram per square centimeter) and BMC (gram) were measured by a whole-body DXA scanner (Lunar Prodigy; General Electric Medical systems, Madison, WI), using an enCORE 2011 version 13.60 (General Electric Medical systems, Madison, WI). Patients underwent DXA scanning for 15 min in a supine position without any movement, in accordance with the manufacturer's recommendations. DXA measurements were performed at baseline and at 1, 6, and 12 mo after commencement of chemotherapy, for all cancer patients. DXA in the control group was performed once at first visit and was compared with the baseline values of the cancer patients. Results were compared with age- and sex-matched reference ranges, and were expressed as the *Z*-score for BMD and BMC according to the manufacturer's reference values in each age group.

Biochemical Analyses

Peripheral venous blood samples were obtained for analysis of serum calcium, phosphorus, and alkaline phosphatase, as well as serum vitamin D. Serum levels of 25-hydroxyvitamin D < 20 ng/mL were considered deficient, whereas levels between 20 and 30 ng/mL were considered insufficient.

Statistical Analyses

SPSS version 20 (IBM Corp., Armonk, NY) was used for data analyses. All values are expressed as median (range). The Kruskal–Wallis method was used for nonparametric analysis of continuous variables among the 3 groups. Wilcoxon *t*-tests were used to compare the medians of paired data. Multiple regression analyses were used to evaluate the factors affecting the bone mineral status of the subjects. Generalized estimation equation (GEE) analyses were used to show trends in bone mineral status after short- and long-term follow-up, using the time points of baseline and 1, 6, and 12 mo, during the first year of cancer treatment. The level of significance was set at $p < 0.05$.

Ethics

Informed consent was obtained from all subjects and/or their guardians. The present study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-1208/168-006).

Results

Patient Characteristics

Descriptive characteristics of the 30 pediatric cancer patients and 30 healthy controls are listed in Table 1. There