Quantitative ultrasound detects bone changes following bone marrow transplantation in pediatric subjects with hematological diseases: A longitudinal study

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ABSTRACT. Background: Bone marrow transplantation (BMT) is associated with bone morbidity. We investigated bone status with quantitative ultrasound (QUS) in pediatric patients with hematological diseases prior to and up to 3 yr following BMT. Methods: Phalangeal QUS measures for amplitude-dependent speed of sound (Ad-SoS) and bone transmission time (BTT) were obtained in 40 hematological patients (25 with malignant, 15 with non-malignant disease; 9.7±4.9 yr) before BMT and 6, 12, 24, and 36 months after BMT. Bone parameters were expressed as Z-scores based on age-sex-matched normal controls. Results: Mean Ad-SoS and BTT Z-scores were normal before BMT and reduced at 36 months (analysis of variance: p=0.0542 and p=0.0233). Ad-SoS and BTT Z-scores remained relatively stable in the first 6 months after BMT and then progressively decreased reaching a plateau at 12-36 months. In non-malignant patients, BTT Z-score decreased at 6-12 months (p=0.029) and subsequently increased, while in malignant patients BTT Z-score showed a decrease at 12-24 months. Pre-pubertal subjects displayed a drop of BTT Z-Score values at both 12 (p=0.023) and 36 months after BMT (p=0.049), while BTT Z-score remained relatively unchanged in pubertal subjects. Early impairment of BTT Z-score was found in patients who suffered acute graft versus host disease (GVHD) compared to patients without this clinical condition; BTT Z-score was lower at 36 months (p=0.045). Conclusions: Longitudinal assessment by QUS of pediatric BMT survivors evidenced that bone status is mildly affected up to 36 months after BMT, mainly in malignant patients, in pre-pubertal subjects at BMT and in patients who suffered acute GVHD.

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INTRODUCTION

The risk of bone loss after bone marrow transplantation (BMT) appears to be multifactorial, related to pre- and post-transplant treatments (1-6), underlying hematologic disease, multiple endocrine dysfunctions, graft versus host disease (GVHD), and general health conditions after grafting (3, 7-11). In adults cohorts, a recent overview of about 15 prospective studies showed a generalized bone pattern characterized at an early stage by the reduction of bone mineral density (BMD) at both vertebral and femoral sites, followed by recovery of BMD at predominantly trabecular bone, and a bone loss persistence in predominant cortical bone up to 48-120 months after BMT (12). In pediatric cohorts, dual X-ray absorbiometry (DXA) and quantitative computed tomography studies have shown a slight but significant reduction of BMD after BMT as well (13-15), and we recently found that also phalangeal quantitative ultrasound (QUS) bone parameters were decreased to a similar extent in children and adolescents evaluated up to 36 months after BMT (16). However, the limitation of these data lies in their cross-sectional study design. Indeed, it has become evident in longitudinal studies that bone loss is a dynamic and long-term complication in pediatric solid organ recipients (17, 18); yet, the temporal sequence of bone loss and its potential for recovery in pediatric bone marrow recipients have not been analyzed.

To address this question, we investigated bone status by hand-phalangeal QUS in 40 children and adolescents with hematological diseases prior to and up to 3 yr following BMT. The aim of our study was: a) to investigate the pattern of amplitude-dependent speed of sound (Ad-SoS) and bone transmission time (BTT) over time; and b) to analyse the effects of disease-treatment- and patient-specific variables on bone QUS parameters and status.

PATIENTS AND METHODS

Study design

This was a longitudinal observational study carried out in a cohort of pediatric subjects affected by malignant or non-malignant hematological diseases, after appropriate approval by the Ethics Committee of the hospital institutional board. Patients were enrolled if they were candidates for BMT and evaluated at baseline and 6, 12, 24, and 36 months after BMT. Subjects with Down syndrome were considered ineligible. All subjects were recruited from a single Pediatric Hematology/Oncology Department in San Matteo Hospital in Pavia, Italy, where they underwent BMT. Informed written consent was obtained from parents and, where applicable, from patients, prior to involvement in the study.
Subjects
We evaluated 40 patients affected with hematological diseases; 19 females (F) and 21 males (M), 9.7±4.9 yr of age (range 2.7-21.8 yr). Twenty-five were affected with malignant disease (no.=11 F and no.=14 M) and 15 (no.=7 M and no.=8 F) with non-malignant disease (Table 1); 37 of them underwent an allogeneic BMT and 3 an autologous BMT. A total of 132 phalangeal QUS assessments were performed with a mean number of evaluations per patient over the study period of 3.3. During the follow-up, 9 malignant patients died from BMT complications between 6-12 months after BMT; 4 malignant subjects were excluded after the 6-month evaluation as they underwent a second BMT because of loss of the primary BMT; and 4 patients (1 malignant and 3 non malignant) were lost at different time points of follow-up. Consequently, 23 subjects were evaluated up to 36 months after BMT. Clinical features, fractures, endocrine dysfunction, pubertal status, total body irradiation (TBI), and GVHD characteristics of the study population are summarized in Table 1. Two patients reported traumatic fractures before BMT (1 F affected with lymphoblastic leukemia had two bone events and 1 M with Diamond Blackfan syndrome had one).

Anthropometric measurements
All patients underwent a physical examination with height and weight measurements and Tanner staging by the same expert in-vestigator (N.D.I.). Subjects were classified pre-pubertal [Gonad 1 (G1) or Breast 1 as (B1)], pubertal (G2-G4 or B2-B4) or sexually mature (G5 or B5) for each sex according to Tanner (19). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m2) and both height and BMI were expressed in SD scores (SDS) using a digital calculator based on Tanner normative data (19).

QUS study
QUS measurements were evaluated using a DBM Sonic 1200 ultrasound device (IGEA, Carpi, Italy) at the distal end of the proximal phalangeal diaphysis of the last four fingers of the non-dominant hand (20). The measurements of Ad-SoS (m/sec) and BTT (μs) through the proximal phalanges were obtained by the same trained investigator (N.D.I.). Ad-SoS and BTT Z-scores were calculated based on our published normative age- and sex-matched values for Italian children and adolescents (20). The intra- and inter-coefficients of variation were calculated to be 0.55% and 0.83% for Ad-SoS, and 0.81% and 1.47% for BTT, respectively (20).

Statistical analyses
Student’s t test for unpaired data was used to compare mean values between genders and between subgroups with different clinical characteristics [malignant/non-malignant diagnosis, TBI, acute GVHD (aGVHD), chronic GVHD (cGVHD), pubertal status at diagnosis and at BMT, hormone deficiency] and simple correlations to investigate the association between QUS measures and chronological (age at study, at diagnosis, and at BMT) or anthropometric parameters (height SDS and BMI SDS). Analyses of variance (ANOVA) were obtained to test the influence of time on bone parameters. Line chart box plots expressing the mean values±SE were used to evidence the pattern of bone parameters and anthropometric measures over time in the overall population and in specific clinical subgroups (malignant/non-malignant subjects, pubertal/pre-pubertal subjects at BMT, aGVHD yes/no). The StatView® statistical software (SAS Institute Inc. Cary, NC, 27513, USA) was used for these analyses. Quantitative variables are expressed as mean±SD.

RESULTS
Subjects
At baseline, 62.5% of the cohort was affected with a malignant disease and 37.5% with a non-malignant disease; 57.5% was pre-pubertal at BMT while 42.5% was pubertal. Fifty-seven percent of the entire cohort was evaluated up to 36 months after BMT (44% of the subjects affected with a malignant disease and 80% of the patients with a non-malignant disease). Age at diagnosis and at the time of evaluation and transplantation, as well as length of follow-up, height and BMI SDSs showed no differences between females and males. Non-malignant patients, regardless of gender, were younger at diagnosis and shorter both at baseline and at follow-up compared to malignant patients (Table 2).

QUS parameters
Mean Ad-SoS and BTT Z-scores were normal before BMT (0.28±1.24 and 0.04±1.10 Z-scores, respectively) and reduced at 36 months (-0.29±1.51 and –0.37±0.98 Z-scores, respectively). As there was no significant differences between F and M for mean QUS parameters at baseline (Ad-SoS Z-score: 0.50±0.93 vs 0.31±1.27 in females and males, respectively; BTT Z-score: 0.08±1.50 vs 0.32±1.23 in F and M, respectively, p=ns). TBI: Z-scores: 0.31±1.27 vs 0.40±1.23 for F and M, respectively, p=ns) or at follow-up (data not shown), analyses were performed across the overall cohort. ANOVA analyses demonstrated that length of time after BMT had a significant negative effect on both Ad-SoS (p=0.05) and BTT Z-scores (p=0.02). Regardless of clinical diagnosis, Ad-SoS and BTT Z-scores remained relatively stable in the first 6 months after BMT and then progressively decreased reaching a plateau at 12-36 months (Fig. 1A). The pattern of height SDS over time seemed