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Are Survivors of Childhood Acute Lymphoblastic Leukemia at Increased Risk for Low Bone Mass?

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Abstract

Acute lymphoblastic leukemia is the most prevalent cancer in children. As an increasing number of cancer survivors reaches adulthood, there may be consequences of the treatment, and there is an issue if low bone mass might be included as a significant late effect. Acute lymphoblastic leukemia patients may have their bone mass compromised during therapy and many years after its withdrawal, but the degree of bone mass decline or recovery are not well elucidated to date. Survivors of stem cell transplantation for leukemia have additional risk factors for bone loss and should be evaluated with caution. Our target is to make a warning about the difficulties in assessing and interpreting bone mass in children and adolescents, the limitations in this assessment in acute lymphoblastic leukemia young survivors (including survivors of stem cell transplantation), the possibility of misdiagnoses, the reasons (if there are any) of low bone mass in this particular group of cancer survivors, as well as consider the therapeutic issues available.

Keywords: Precursor cell lymphoblastic leukemia-lymphoma/ complications; Bone marrow transplantation; Bone density

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most prevalent cancer in children [1]. As an increasing number of cancer survivors reaches adulthood, there may be consequences of the treatment, including adiposity, metabolic syndrome traits [2-9] and occasionally low bone mass [10-18], which is a condition not totally understood, so far.

Several pediatric conditions may have an increased risk for low bone mass, which is attributed to the disease itself, genetic characteristics, intensive therapy against the disease [10-19], as well as body composition modifications [20]. Cancer survivors, particularly ALL patients, are part of one of these important groups and there are several important concerns regarding their bone heath [10-19]. Low bone mass has been observed in all phases of the disease: at diagnosis, during treatment, and throughout the post-treatment period for as long as 20 years [21]. Firstly, pain in the bones or joints is one of the important initial symptoms of the disease. Moreover, low bone mass might be the only manifestation of underlying childhood ALL [22]. Throughout chemotherapy, Avascular Necrosis (AVN) is a disabling complication in children and adolescents, especially secondary to steroids [23]. During therapy and many years after its withdrawal, low bone mass may be a consequence of therapy/disease; however, the degree of the decline of bone mass and its recovery are not well elucidated yet [10-18,21].

This paper discusses the difficulties of assessing and interpreting bone mass in children and adolescents, the limitations on this assessment in ALL young survivors, the particularities of survivors of hematopoietic Stem Cell Transplantation (SCT), the possible reasons of low bone mass in this group of cancer survivors, as well as some therapeutic issues.

Assessment and Interpretation of Bone Mineral Density in Pediatric Patients

There are many issues to be addressed as regards bone mass loss in pediatric patients. First of all, there are two important methods to assess changes in Bone Mineral Density (BMD): Dual-energy X-Ray Absorptiometry (DXA), and peripheral quantitative Computed Tomography (CT). Even though the CT study allows the assessment of structure, to date DXA is the most important technical method to evaluate BMD in children and adolescents [24-28].

Furthermore, it is important to elucidate that even DXA has important technical limitations. Height Z scores and BMD Z scores have a direct relation in normal and healthy children and adults, which is technical, caused by the fact that DXA does not measure true density (bone mass/volume), but only areal BMD (bone mass/projection area) [24-28]. This means that short stature could influence the results. Therefore, the International Society of Clinical Densitometry states that DXA evaluation in pediatric subjects who have not completed puberty or linear growth need size correction, or should be interpreted according to bone age, and not chronologic age. In children with linear growth or maturational delay, spine and Total Body Less Head (TBLH) Bone Mineral Content (BMC) and areal BMD results should be adjusted for absolute height or height age, or compared with pediatric reference data that provide age-, gender- and height-specific Z scores [24-28]. Moreover, it is also important to state that the Z scores are used in the comparison of DXA results with the normal population with the same age and sex, for children, adolescents and young adults, while T scores are utilized only for men at or above 50

years of age and women during menopause, and should not appear in pediatric DXA reports. Beyond that, following the guidelines of the International Society of Clinical Densitometry, the radiography of the lumbar spine is not accepted as a diagnostic method of low bone mass, and should only be used in the evaluation of rarefaction of the bone and to perform vertebral fracture assessment [24-28].

Yet another important issue to be addressed is that the diagnosis of osteoporosis should not be done on the basis of densitometric criteria alone, but requires both a clinically significant fracture history and low bone mass. Thus, the terms "osteopenia" and "osteoporosis" should not appear in pediatric DXA reports without a clinically significant fracture history. "Low bone mass for chronologic age" is the preferred terminology when either the BMC or the BMD Z score are less than or equal to -2.0. In patients with primary bone diseases or potential secondary bone diseases (eg, due to chronic inflammatory diseases, endocrine disturbances, history of childhood cancer, or prior transplantation [nonrenal]), spine and TBLH BMC and areal BMD should be measured at clinical presentation. In addition, therapeutic interventions in children and adolescents should not be instituted on the basis of a single DXA measurement, and the minimal time interval for repeating a DXA to monitor treatment or a disease-process is six months [24-28].

The hip (including total hip and proximal femur) in growing children is not a reliable site for measurement due to significant variability in skeletal development and lack of reproducible regions of interest. Moreover, there is no data on Z scores for total femur BMD for patients over 20 years of age (National Health and Nutrition [NHANES] III 1988-1994) [12,17,24-28].

While the quantity of bone mass can be estimated by measuring BMD using DXA, its measurement does not capture all the risk factors for fracture. Quantitative changes in skeletal turnover can be assessed non-invasively by the measurement of serum and urinary biochemical markers, such as serum osteocalcin, bone specific alkaline phosphatase, the N-terminal propeptide of type I collagen for bone formation, and the crosslinked C- (CTX) and N- (NTX) terminal telopeptides of type I collagen for bone resorption. In postmenopausal osteoporosis, levels of bone resorption markers above the upper limit are associated with an increased risk of fracture, independent of BMD. Therefore, the combined use of BMD measurement and biochemical markers is helpful in fracture risk assessment, especially in those women who are not identified as at risk by BMD measurement alone. Nonetheless, it is not known the real meaning of increased bone turnover markers in children and adolescents and their relationship with bone mass, as they are a growing population, and are in the process of bone mass acquisition. In addition to diagnosis and fracture risk prediction, the levels of bone markers may also monitor antiresorptive therapies, as their values decrease rapidly after 3-6 months of therapy, being more strongly associated with fracture outcome than changes in BMD [29-31].

Assessment and Interpretation of Bone Mineral Density in Young Survivors of Childhood Acute Lymphoblastic Leukemia

Children treated for cancer, particularly ALL, may have their bone mass compromised by several factors [10-20].

Nonetheless, the same technical limitations regarding interpretation of DXA in children and adolescents are of extreme importance while measuring BMD in children and adolescents treated for cancer. The first important concern is the requirement of adjusting DXA output in survivors of ALL, with a body size (weight and/or height) correction which derived BMC for bone area. After the correction many patients previously considered with low BMD Z scores are in fact at normal limits [12,24-28,32-37]. Secondly, it is important to establish local norms with DXA and not rely on the ranges provided by the manufacturers of densitometers [35,38]. Body mass index (BMI) is not a good nutritional index in cancer population, and to date DXA provides not only the bone mass but also body composition, comprising fat mass and bone-free lean mass [35]. So far, the relationship between body composition and bone mass is little understood, but surely there is a strong connection between both tissues [19,20].

Causes of Low Bone Mineral Density among Acute Lymphoblastic Leukemia Survivors

The pathogenesis of decreased BMD in childhood cancer is clearly multifactorial and it is dependent not only on the disease/therapy, but may also involve the host genetic characteristics [11,19,21,34]. Several risk factors may influence bone acquisition, as well as bone mass resorption. Leukemic invasion of bone is sometimes the first symptom of the disease. Therapy with methotrexate and particularly with corticosteroids is one of the most important factors which can interfere with bone metabolism. Other factors include irradiation and other hormonal deficiencies, especially of Growth Hormone (GH) and gonadotropins [11,21,39-42].

Cranial radiation therapy (CRT) at or above 24 Gy, craniospinal irradiation and total body irradiation (TBI) are some of the primary predictors of suboptimal BMD in ALL survivors [11,39-41]. Low lumbar spine BMD was also associated with male or female gender, white race, lower BMI, and cumulative doses of glucocorticoid of at or above 5,000 mg [41,42]. GH deficiency, mostly after CRT, may lead to several negative effects on bone mass, so that 25 years after diagnosis, GH-deficient ALL patients may experience a decrease in Z scores at femoral neck [41,42].

In addition, nutritional problems should also be taken into account, as they might interfere with calcium and vitamin D metabolism, as well with several polymorphisms in vitamin D receptors, calcitonin, collagen type I alpha 1 (COLIA1), estrogen receptor 1, and corticotropin releasing hormone receptor 1 (CRHR1), which have an impact on AVN development, and could get involved with corticoid effect and genetic background determining an individual tendency to decreased bone mass [21,43,44].

In summary, ALL patients may show a deficit in both trabecular and cortical bone deposition related to host profile (chronological age, sex and genetic predisposition), disease characteristics (risk for recurrence of the disease), direct effects of chemotherapy (methotrexate and glucocorticoids) and/or CRT, in addition to possible hormone deficiencies (gonadal failure or GH insufficiency) [10-18,39-45].

What actually seems to occur is a decrease in BMD in childhood ALL patients during therapy, even with current protocols based solely on intensive chemotherapy, increasing the risk of fracture during that period, but usually recover, returning to normal ranges, corresponding to the two years after the completion of treatment [46]. This recover of bone mass coincides with the end of the period known as the adiposity rebound, in which occurs an increase in all the adiposity indexes, corresponding to the two years following therapy withdrawal [20].

ALL survivors may experience changes in adiposity during and throughout treatment, which may influence bone mass acquisition and decline [19,20,47]. Adiposity has been considered as beneficial for bone health due to the positive effect of mechanical loading conferred by body weight on bone formation [48-50]. Nonetheless, some of the factors that are released by peripheral fat accumulation into the circulation (adipokines and inflammatory markers) may in turn have a deleterious effect on bone mass. "Osteopenia/osteoporosis", sarcopenia, and obesity are commonly observed in the process of aging, and recent evidence suggested a potential interconnection of these conditions with common pathophysiology, even though this interaction is still poorly understood [51-56]. So far, few studies have evaluated the relationship between adiposity, including adipokines, and BMD among ALL survivors [47,56].

To date, there are several cross-sectional studies as regards bone mass in long-term ALL survivors, but few longitudinal data, especially in relation to the prevalence of fractures [10-18,46,57].

The prevalence of low BMD in adult survivors of childhood ALL, and the degree of decline or recovery, are not well elucidated yet [11]. An important point to be emphasized is that the majority of adult long-term ALL survivors present BMD at the normal limits [11,42]. Results from the St. Jude Lifetime Cohort Study showed that very low BMD is relatively uncommon in adult survivors of childhood ALL, and BMD Z scores tended to improve from adolescence to young adulthood [11].

Survivors of Hematopoietic Stem Cell Transplantation: A Special Group to be considered

In what regards survivors of hematopoietic SCT for leukemias, bone mass is an extremely important issue to be addressed as this subgroup of patients have additional risk factors for bone loss while compared to ordinary leukemia survivors. Firstly, this special and growing population have mixed health problems, habitually underwent multiple and different chemotherapy protocols (including myeloablative conditioning) and/or radiation treatment schedules (including TBI) previously to SCT, that might lead to decreased gonadal function and fertility, which is one of the most important factors in determining reduced BMD in these patients [40,58]. Secondly, after SCT these patients receive immunosuppressive regimens with glucocorticoids, and they might develop several complications, including graft-versus-host disease (GVHD), which requires additional long-term excessive dose of glucocorticoids, and consequently aggravate bone loss and the risk for AVN [58,59].

Bone loss has been observed within the first six months in both children and adults after SCT. While there is some evidence that bone formation may be reduced in children after SCT due to all the factors already discussed, bone resorption is also increased, evidenced by elevated bone turnover markers, leading to the pathophysiology of bone loss after pediatric SCT [60]. On the other hand, ALL subjects who had previously undergone allogeneic SCT, even without any treatment inducing low bone mass, also presented with decreased BMD values and increased skeletal turnover five years after the transplant, leading to an increased risk for vertebral fracture [61].

Therapeutic Issues

Considering therapeutic issues to improve BMD, cholecalciferol and calcium supplementation provides no added benefit to nutritional counseling for improving lumbar spine BMD among adolescent and young survivors of ALL [42]. A high prevalence of vitamin D insufficiency (serum 25-OH-vitamin D<30 ng/mL) has been detected, but was not associated with BMD outcomes, and similar to what has been described in the general population [42,62,63]. Thus, vitamin D insufficiency could not be attributed to ALL itself or its therapy [62,63]. Even though little is known about dietary and nutrient intake as regards bone heath in long-term survivors of childhood ALL, it is always advisable to maintain careful dietary intervention to optimize bone health in this group of patients, so that vitamin D deficiency should be corrected to achieve a serum 25-hydroxyvitamin D concentration of at least 20 ng/mL, patients should receive calcium and treat secondary hyperparathyroidism (if detected), particularly those patients who undergone SCT [62-64].

On the other hand, GH therapy during two years in young adult survivors of childhood ALL improved BMD and body composition, with BMD and lean mass showing an increase, while fat mass decreased [39,41].

Based on the good results obtained in patients with osteogenesis imperfecta, drugs such as the bisphosphonates can clearly inhibit bone resorption when used in children either receiving anti-leukemic therapy or many years after the completion of therapy, even though the great experience is during ALL chemotherapy [23,65-72].

Firstly, alendronate, which is a group of oral bisphosphonates, has been used in children undergoing therapy for leukemia or non-Hodgkin`s lymphoma (maintenance phase) and to date retrieved good results. The reports showed a positive impact upon mineral metabolism with a significant gain in Z score for whole BMC and also at lumbar spine. Biochemical evaluation of bone mineral metabolism through bone turnover markers also showed a change in bone turnover favouring the formation over bone resorption. In addition, some improvement of motor function was observed, even though there were modest gains in quality of life [65,66].

Data regarding the effects of pamidronate on the developing skeleton are limited, but a growing body of evidence supports the safety and efficacy of this medication in pediatric bone metabolic disease. The impact of the interaction between ALL and pamidronate is not known. Few short term side effects have been described during pamidronate infusion, such as hyperpyrexia and hypocalcemia (non-symptomatic). Potential short and long term benefits of its use on bone health deserve further studies [67]. There are only few studies evaluating the effects of pamidronate in ALL patients with low BMD during therapy, but they had shown positive results upon bone turnover and either modest or positive effects on BMD [68,69].

The use of pamidronate has been much more frequent among those patients who present with bone disease at the diagnosis of leukemia, particularly those with vertebral fractures, usually characterized by a decrease in bone formation, resulting in pain and loss of ambulation. Even though the treatment of underlying leukemia was of primary importance in decreasing pain and restoring normal bone mass, pamidronate therapy resulted in pain control, improved function and prevented new fractures [67].

Moreover, pamidronate may also ameliorate pain scores and musculoskeletal function in patients with AVN occurring as a complication of childhood ALL therapy, even though objective radiologic benefits could not be demonstrated so far [70-72].

Currently, the effect of Zoledronic Acid (ZA), a third generation bisphosphonate, was evaluated as the treatment of chemotherapy related AVN and joint pain, showing no significant effect on AVN of the hips. Many patients required arthroplasty, despite bisphosphonate treatment, while patients with AVN of the knees had radiological stabilization. The response depended on underlying etiology and general condition of the patient and also on the severity and type of joint involvement at the start of therapy. So far, lumbar spine BMD showed an increase after one year of treatment [23,71,72].

Notwithstanding, the preventive use of ZA might potentially mitigate this side effect of current treatment regimens and is worthy in this sense, as this group of children are at risk of developing low bone mass during treatment; however, this bisphosphonate prophylaxis requires further evaluation, as this approach has been questioned by other authors [23,71,72].

Considering the six months after SCT, if bone loss is detected, treatment is indicated in the immediate posttransplantation period. Intravenous bisphosphonates (particularly ZA) are the most promising approach for the management of transplantation low bone mass and AVN, partly by increasing the osteogenic progenitors in the stromal cell compartment, even though their role has not been completely established. Treating hypogonadism also increases BMD and decreases bone turnover markers in this subgroup of patients [64,73,74].

Conclusions

Bone mass should be interpreted with caution in ALL young survivors. Recent data confirm that low bone mass might be present during therapy, even with current protocols based solely on intensive chemotherapy. The risk of fracture is increased, but usually recovers two years after the completion of treatment, tending to improve from adolescence to young adulthood, reflecting the time necessary to mineralize newly formed bone. To date, there are few longitudinal data in relation to the prevalence of fractures. Nonetheless, very low BMD is relatively uncommon in adult survivors of childhood ALL. The use of bisphosphonates during anti-leukemic therapy and after the completion of treatment might prevent or treat low BMD in ALL survivors, but to date further studies are required in the context of randomized clinical trials.

On the other hand, SCT survivors have additional risk factors for bone loss, including gonadal dysfunction, and excessive long-term steroid therapy. This particular subgroup should be evaluated with caution because further rapid bone loss will occur in the first several months after transplantation, and treatment if necessary should be initiated in the immediate posttransplantation period.

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