Osteoporosis in Survivors of Acute Lymphoblastic Leukemia

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Key Words. Acute lymphoblastic leukemia · Childhood cancer · Osteopenia · Osteoporosis · Survivors

ABSTRACT
Osteoporosis is currently receiving increasing attention as an important late effect in survivors of childhood cancer and its treatment because of their quality of life and its negative effect on the survivors’ ability to perform developmentally appropriate activities. Survivors of childhood cancer are especially vulnerable because they are affected during childhood and adolescence, a time when peak bone mass should be achieved. This paper reviews decreased bone density in acute lymphoblastic leukemia (ALL), which is the most common childhood cancer and has a cure rate approaching 80%. Osteopenia/osteoporosis 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. Among the findings that have been described are musculoskeletal pain, disturbed gait, fractures, kyphosis, lordosis, and growth failure. Risk factors not specifically related to ALL include smoking, ingestion of carbonated beverages, and family history of “brittle bone” or fractures. Patients should be counseled in regard to diet, exercise, smoking cessation, and avoidance of carbonated beverages. There are a number of options for specific drug therapy; however, the administration of bisphosphonates to children and adolescents must be approached with caution. Research is needed to determine how extensive the problem is and how to best prevent and treat the osteopenia/osteoporosis associated with ALL.

INTRODUCTION
As increasing numbers of childhood cancer patients are surviving into adulthood, the long-term monitoring of this vulnerable population assumes increasing importance [1]. Cancer is diagnosed in approximately 7,500 children under 15 years of age each year in the United States [2], and, overall, better than 70% will be cured of their cancers [1, 2]. Most long-term survivors, except for some who have had radiotherapy or surgery for central nervous system involvement or certain sarcomas, do not have apparent physical defects [3, 4]. Similarly, the majority appear to have no more psychosocial difficulties than their peers [5, 6]. Although the early sequelae of childhood cancers are fairly well defined, later effects may become evident only after many years have passed. When such effects occur, they can interfere with the ability to participate in developmentally appropriate activities and impair the survivors’ health-related quality of life [7]. Unfortunately, childhood cancer patients are often lost to follow-up as they mature into middle and old age. The National Cancer Institute reported that 51% of 14,000 long-term survivors of childhood cancer were not followed up appropriately [8].

Among the possible serious late effects from cancer and its treatment are second cancers, cardiac dysfunction, and hepatitis C, as well as infertility, growth failure, endocrine deficiencies, renal damage, pulmonary toxicity, defects of vision, hearing loss, dental changes, musculoskeletal abnormalities, obesity, and neuropsychiatric problems [3, 4]. Decreased bone mineral density (BMD), which can lead to fractures, deformity, pain, and a substantial financial burden [9, 10], has also been recognized in child cancer patients [11-20] and, more specifically, acute lymphoblastic leukemia (ALL) patients [21-48].

ALL, the most common form of childhood cancer, accounts for one-fourth of all childhood cancers [49-51]. Because the current cure rate approaches 80% [51], approximately 1,500 children in the U.S. are cured of ALL each year [51]. This review focuses on the prevalence and importance of osteopenia and osteoporosis in survivors of childhood ALL.

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Received April 30, 2001; accepted for publication May 10, 2001. ©AlphaMed Press 1083-7159/2001/$5.00/0

SYMPTOMS AND SIGNS
Among the symptoms related to decreased BMD are musculoskeletal pain, especially in the extremities, spine, and pelvis; abnormal gait; kyphosis and lordosis; unusual fractures; and decreased or delayed linear growth. Bone pain is a common presenting sign in children with ALL. It is not uncommon for an ALL patient, when first seen, to limp or even refuse to walk. Musculoskeletal pain has been reported in 21% to 59% of children [30, 42]. Children with bone pain do not always have apparent radiologic lesions, and many children with skeletal changes do not have pain [30, 40, 42]. Bone pain is caused by pressure from infiltration of leukemic cells into the medullary cavity or under the periosteum, while joint pain is usually thought to be referred from lesions of the periosteum [30]. However, 14% of patients with acute leukemia and joint pain studied at the National Institutes of Health by Thomas et al. [42] had concurrent erythema and swelling of the painful joints. Joint pain is frequently migrating in character [41], sometimes leading to an initial presumptive diagnosis of rheumatic fever, juvenile rheumatoid arthritis, or septic arthritis. Fractures can occur at the time of diagnosis, as well as during and after ALL therapy, frequently long after cessation of therapy. Rogalsky et al. [36] reported fractures in 25% of children with acute leukemia, 12% pathological, and 13% following trauma, during the course of their disease. Halton and Atkinson [28, 29] reported that 39% of children with ALL had fractures by completion of therapy. The literature contains many case reports of vertebral compression fractures [32, 33, 37, 39]. Thomas et al. [42] observed impairment of bone growth during the active disease process in children with acute leukemia who had normal height at diagnosis; bone growth resumed with the onset of remission [42].

BONE METABOLISM
About 10% of bone is normally replaced each year [9, 10]. Bone metabolism is a continuous cycle of modeling (resorption followed by formation at a distant skeletal site) and remodeling (resorption followed by formation at the same skeletal site). Osteoclasts (derived from cells of monocytic lineage) function to resorb existing bone, while osteoblasts (derived presumably from hematopoetic stem cells) lay down replacement bone matrix. Cortical bone, the dense outside protective surface of bone, makes up about 80% of the skeleton; and trabecular or cancellous bone, the spongy-appearing inner portion, makes up the other 20%.

BMD increases with age during the first two decades of life until peak density is reached by around 20-25 years of age. It remains fairly constant thereafter until, in women, a rapid phase of estrogen-dependent bone loss occurs starting shortly after menopause, lasting 5 to 10 years, followed by a less rapid phase of age-related bone loss. Although men do not experience a rapid phase of bone loss, they also have age-related bone loss. The ultimate outcome depends upon previous peak bone mass and the rate of bone loss [9]. The financial cost of osteoporosis in the U.S. has been estimated as approximately $10 billion each year [9, 10].

Normal bone mass is defined by the World Health Organization as BMD within one standard deviation (SD) of the young adult mean; osteopenia as increased bone loss, with bone mass between 1 and 2.5 SDs below normal; and osteoporosis as bone mass ≥2.5 SDs below normal [52, 53]. For every SD by which BMD is below peak bone mass, fracture risk increases by a factor of 1.5 to 3.0 [9].

Given that adequate supplies of calcium and vitamin D are essential for normal bone growth, bone metabolism is regulated by a complex system of factors and hormones [10]. Fibroblast growth factors, insulin-like growth factors (IGF) or somatomedins, transforming growth factors, and platelet-derived growth factors stimulate osteoblasts. Various prostoglandins influence both osteoblasts and osteoclasts. Colony-stimulating factors are involved with osteoclast proliferation. The mechanisms of action for the various hormones involved in bone metabolism are described in Table 1. Hyperthyroidism and hyperparathyroidism accelerate bone loss, as do cortisol and related steroids. Estrogen and testosterone hormone deficiencies also result in accelerated bone loss. Calcitonin, on the other hand, inhibits bone resorption and has been used to treat increased bone loss, as in the hypercalcemia of malignancy and Paget’s disease.

RISK FACTORS FOR OSTEOPOROSIS
Because the pathogenesis of decreased BMD in childhood cancer patients is multifactorial, a number of risk factors must be considered. Leukemic invasion of bone is not uncommon in ALL [21-48]. Other risk factors for osteoporosis include corticosteroid [54] and methotrexate therapy [55-61]; local and cranial radiation [62, 63]; and deficiency of various hormones [64]. Decreased activity [25] because of limited exercise capacity and physical inactivity, as well as nutritional deficiency [28] resulting in altered calcium, vitamin D, and magnesium metabolism, must be given consideration. Male sex and Caucasian race appear to be additional risk factors in childhood cancer patients [24].

DIAGNOSTIC METHODS

History
Age, sex, and race should be recorded. Questions should be asked about nutrition (calcium intake [65, 66], vitamin D supplementation [66], consumption of carbonated beverages
Osteoporosis in ALL Survivors

Carbonated beverages, presumably because of their phosphate content, have been associated with fractures in physically active girls [67, 68], and smoking has been shown to increase bone loss [69]. Other questions should be about exercise (minimum 30 minutes three times weekly) [70, 71], symptoms of musculoskeletal pain, gait disturbances, history of fractures, kyphosis or lordosis, and family history of “brittle bones” or fractures.

**Physical Examination**

Height, weight, and pubertal status (Tanner stage) should be recorded. The physical examination should include assessment of the gait and ability to walk; inspection for kyphosis [32] and lordosis [37]; and evaluation of the back and extremities for erythema, swelling, and tenderness [37, 42].

**Laboratory Studies**

Calcium, phosphorus, and magnesium levels, alkaline phosphatase, and vitamin D are useful blood values, as are growth, estrogen, testosterone, thyroid, and parathyroid hormone levels. Urinary hydroxyproline and fasting urinary calcium concentrations, if low, are indicative of bone turnover [10].

**X-Rays**

The varied x-ray manifestations in ALL are characteristic but not pathognomonic [30, 36, 38, 40, 42]. The classical triad of skeletal findings includes transverse radiolucent bands (leukemic lines) across the metaphases of long bones, osteolytic and osteosclerotic lesions, and periosteal reactions. Generalized osteoporosis, vertebral compression, and pathologic fractures are also seen. In children the peripheral skeleton, especially the lower extremities, is most commonly affected, while adults are more likely to have lesions in the axial skeleton [30]. Skeletal lesions are frequently present at diagnosis [21, 22, 35, 39, 40], and are observed as well during treatment [29, 32] and following completion of therapy [25, 33]. A recent study found that children with severe skeletal involvement had a better prognosis than children without skeletal involvement [43]. This is in opposition to previous investigators, who had found that skeletal involvement connoted a poorer prognosis [44, 45] or no prognostic significance [46-48].

**Dual Energy X-Ray Absorptiometry**

Perhaps the most important diagnostic tool in current use for diagnosing osteopenia/osteoporosis is dual energy x-ray absorptiometry (DEXA) [72-75], which assesses the mineral content of the spine while keeping the amount of radiation exposure low [26-28]. The spine is largely made up of trabecular bone. DEXA is therefore more useful than single photon absorptiometry, which is limited to measuring cortical bone density [17, 75]. Clinically important sites for evaluation are the lumbar spine (L2-L4), femoral neck, and Ward’s triangle, the latter describing a region of the proximal femur consisting predominantly of trabecular bone [20, 72]. Normal BMD values for girls and boys 5 to 19 years of age are listed in Tables 2 and 3.

Adult DEXA values, expressed as T-scores, are derived from comparison to the young adult mean BMD [11]. Children’s values are converted to Z-scores, which express

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Effect on bone turnover</th>
<th>Cells affected</th>
<th>Mechanism of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
<td>Increase</td>
<td>Progenitor, osteoblasts</td>
<td>High levels stimulate osteoblasts, increase osteoclast activity</td>
</tr>
<tr>
<td>Thyroxine (T3)</td>
<td>Increase</td>
<td>Osteoclasts</td>
<td>High levels increase resorption, especially cortical bone</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Decrease</td>
<td>Osteoblasts</td>
<td>With deficiency, osteoblasts stimulated, causing increased osteoclast activity</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Decrease</td>
<td>Osteoblasts</td>
<td>With deficiency, osteoblasts stimulated, causing increased osteoclast activity</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Increase</td>
<td>Progenitor, osteoblasts, osteoclasts</td>
<td>High levels increase bone resorption and inhibit bone formation</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Decrease</td>
<td>Osteoclasts</td>
<td>Inhibits osteoclast activity and bone resorption</td>
</tr>
<tr>
<td>Insulin</td>
<td>Decrease</td>
<td>Osteoblasts</td>
<td>Increases IGF-I synthesis in liver, causing increased collagen synthesis by osteoblasts</td>
</tr>
</tbody>
</table>

*Table modified from table of hormones and factors involved in bone metabolism according to Christensen [10].

Table 1. Mechanisms of action for hormones involved in bone metabolism*
deviation from the mean BMD for age and sex [11, 12]. BMD values are changed to Z scores by subtracting the age and sex-specific mean BMD value of the control group from each patient’s BMD value, and then dividing the result by the corresponding age and sex-specific SD [12].

Radiographic evidence of osteopenia was reported by Atkinson and Halton et al. [28, 29] as an initial finding in 13% of ALL patients. During therapy 76% developed radiographic evidence of osteopenia, and 64% developed absorptiometry evidence of reduction in bone mineral content. The initial

### Table 2. Mean BMD values* for female spine (SD = 0.10), femur regions (SD =0.10), and total body (SD = 0.08). BMD expressed as gm/cm².

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>n</th>
<th>Spine</th>
<th>n</th>
<th>Neck</th>
<th>Triangle</th>
<th>Trochanter</th>
<th>n</th>
<th>Total Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>42</td>
<td>0.638</td>
<td>14</td>
<td>0.613</td>
<td>0.726</td>
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<td>8</td>
<td>0.766</td>
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<tr>
<td>6</td>
<td>46</td>
<td>0.662</td>
<td>24</td>
<td>0.643</td>
<td>0.783</td>
<td>0.621</td>
<td>11</td>
<td>0.793</td>
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<td>7</td>
<td>64</td>
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<td>32</td>
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<td>31</td>
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</tr>
<tr>
<td>8</td>
<td>87</td>
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<td>58</td>
<td>0.707</td>
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<tr>
<td>9</td>
<td>68</td>
<td>0.724</td>
<td>34</td>
<td>0.725</td>
<td>0.754</td>
<td>0.630</td>
<td>25</td>
<td>0.835</td>
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<tr>
<td>10</td>
<td>68</td>
<td>0.787</td>
<td>40</td>
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<td>30</td>
<td>0.811</td>
<td>0.802</td>
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<td>0.781</td>
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<tr>
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<td>32</td>
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<td>0.800</td>
<td>20</td>
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<tr>
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<td>1.029</td>
<td>1.013</td>
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<td>33</td>
<td>1.051</td>
<td>1.068</td>
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<td>18</td>
<td>57</td>
<td>1.162</td>
<td>30</td>
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<td>0.965</td>
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<td>28</td>
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<td>0.825</td>
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<tr>
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<td>359</td>
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</tbody>
</table>


### Table 3. Mean BMD values* for male spine (SD = 0.10), femur regions (SD = 0.10), and total body (SD = 0.08). BMD expressed as gm/cm².

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>n</th>
<th>Spine</th>
<th>n</th>
<th>Neck</th>
<th>Triangle</th>
<th>Trochanter</th>
<th>n</th>
<th>Total Body</th>
</tr>
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<tr>
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<td>0.635</td>
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<td>8</td>
<td>0.762</td>
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<td>0.765</td>
<td>0.680</td>
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<td></td>
<td>256</td>
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</tr>
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</table>

finding of osteopenia was attributed to leukemic infiltration, while the subsequent reduction in bone mineral content during therapy was attributed largely to chemotherapy. Other studies have shown that decreased BMD, presumably because of failure to reach an optimal peak bone mass, persists after treatment [23-27], for as long as 20 years [27].

TREATMENT

Intervention designed to improve BMD should insure sufficient supplies of calcium and vitamin D [65, 66], include a weight-bearing exercise program [70], and provide counseling for smoking cessation [69] as well as avoidance of carbonated beverages [67, 68]. Any hormone imbalance that is identified must be addressed, with replacement therapy if appropriate [20, 62, 63, 75]. Drugs currently used for treating osteoporosis specifically decrease bone loss by decreasing bone resorption [9, 76].

Calcitonin, a naturally occurring hormone produced by the thyroid gland, is an osteoclast inhibitor that is used in the form of daily s.c. injections to treat Paget’s disease of bone. It has recently been approved for administration by nasal spray for the treatment of osteoporosis in older women [76], but requires further study for use in children or adolescents.

The bisphosphonates, a class of drugs that inhibit osteoclast activity, are useful in the treatment of osteoporosis. Alendronate has received approval from the U.S. Food and Drug Administration (FDA) and is currently the most commonly used bisphosphonate for the treatment of osteoporosis [77-84]. Because it is poorly absorbed, the drug should be taken on an empty stomach, with eating and drinking delayed for at least 30 minutes. Patients should avoid lying down for at least 30 minutes after ingestion because esophagitis and esophageal hemorrhage have been reported following its use. Its use is not recommended in the presence of renal insufficiency, and liver damage from alendronate has been reported [85]. FDA approval of alendronate does not include children under the age of 18 years, nor does it include pregnant women and girls or women who may become pregnant [86]. Among other bisphosphonates that are useful in treating metabolic disorders are etidronate [87, 88] and risedronate [87, 89].

A slow-release sodium fluoride is currently being studied because of its osteoblast-stimulating property, and low-dose parathyroid hormone is in an early stage of investigation for its anabolic potential [76].

NEED FOR RESEARCH

Osteopenia/osteoporosis occurs in children and adolescents who are treated for cancer at a time when they should be achieving their peak bone mass. In order to determine the extent of the problem, epidemiological studies must include evaluation at the time of diagnosis as well as a prolonged follow-up period. Research concerning general and specific intervention measures for prevention and treatment should be a part of all childhood cancer treatment programs. When children and adolescents receive experimental substances such as calcitonin and the bisphosphonates, particular attention needs to be directed toward the safety of their administration.

CONCLUSIONS

All childhood cancer survivors, especially survivors of ALL, should be monitored indefinitely for the appearance of possible cancer- and treatment-related long-term effects, among them osteopenia/osteoporosis. Counseling for a healthy lifestyle in order to minimize such effects, is an integral component of regular follow-up. Research is needed to determine the extent of osteopenia/osteoporosis among survivors of childhood and adolescent cancer, who are at greatly increased risk for osteoporosis, and to ascertain which are effective measures for attaining optimal BMD.

ACKNOWLEDGMENT

We thank Rita A. Rooney, R.N., M.P.H., of the National Osteoporosis Foundation and Howard Barden, Ph.D., of G. E. Lunar Corporation for supplying information concerning osteoporosis and bone mineral density in children.

REFERENCES


