Safety and efficacy of alendronate to treat osteopenia in children during therapy for acute lymphoblastic leukemia. A retrospective cohort study of sequential outcomes.

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Abstract

Background. Low bone mineral density (osteopenia) is encountered in children with acute lymphoblastic leukemia (ALL) before, during and after treatment. Prior experience with alendronate, an oral bisphosphonate, demonstrated high tolerability and evident clinical efficacy. However, concerns have been expressed about the long-term safety and utility of such agents in children. Procedure. Of 217 children with ALL treated on Dana Farber Cancer Institute protocols 69 received alendronate for a mean of 87 weeks after dual energy X ray absorptiometry (DXA). DXA was repeated following completion of alendronate, and again 5-9 years later in a subgroup of 32 children. Lumbar spine areal bone mineral (LS aBMD) Z scores were obtained and values corrected for height, age and weight (HAW) were calculated for subjects 3-18 years of age. Results. Almost 80% (N=172) of the children remain in continuous complete remission at a mean of 14.5 years from diagnosis. Of those who receive alendronate, which was almost uniformly well tolerated, 7/69 (10.3%) relapsed compared to 19/89 (21.3%) who did not receive the drug. The mean unmodified LS aBMD Z score rose from -1.78 to -0.47. This gain was statistically significant for both unmodified (p <0.0001) and HAW corrected Z scores -1.32 to -0.42; p <0.0001). There was a modest median loss of LS aBMD (Z score 0.045) subsequently in the subgroup (N=32) of subjects on long-term follow up. Discussion. Alendronate appears to be well tolerated and moderately effective in osteopenic children with ALL. Whether it offers protection against relapse of leukemia needs further study.

Introduction

Bony morbidity is common in children with acute lymphoblastic leukemia (ALL). Pain is a frequent symptom at diagnosis,¹associated with an expanding cell mass in the medullary cavity, and vertebral fractures at this time are prominent and often unrecognized clinically.² Osteopenia, reflecting loss of bone mineral, is demonstrable before the initiation of therapy³ and becomes more evident with the onset of treatment.⁴ The contributing factors include glucocorticoid and methotrexate medication, cranial irradiation (now used much less frequently) and reduced physical activity.⁵

Additional bony morbidity is seen in the form of osteonecrosis that shares an etiology with osteopenia, from exposure to high cumulative doses of corticosteroids, although the pathogenesis is different.⁶ Both osteopenia⁷ and the symptoms of osteonecrosis⁸ may be ameliorated by the administration of bisphosphonates.

These compounds are structural analogues of natural inorganic pyrophosphate which explains their very high affinity for bone because they bind to crystals of hydroxyapatite and impede their breakdown, so suppressing

bone resorption.⁹ The third generation bisphosphonates, including alendronate and pamidronate, have side chains containing nitrogen. These agents bind to and inhibit farnesyl pyrophosphate synthase, an important enzyme in the mevalonic acid pathway. In turn this results in dysregulation of osteoclast metabolism with eventual apoptosis.⁹ Bone resorption remains suppressed for the duration of treatment. With oral agents only about 50% of the absorbed dose is retained in the skeleton, the remainder being excreted in the urine. The amount of bisphosphonate retained varies considerably among patients and between clinical disorders, probably reflecting variations in bone turnover.⁸

In our preliminary experience from 2000, intravenous pamidronate was effective in redressing the depletion of bone mineral but poorly tolerated;¹⁰ however, oral alendronate, with 5 fold greater potency,⁹ was well tolerated and retained clinical efficacy,¹¹ despite low bioavailability.¹²

Nonetheless, concerns have been expressed about the safety and efficacy of bisphosphonates in children.¹³ While there have been no reports in childhood of the uncommon but dramatic problem of osteonecrosis of the jaw encountered in adults,¹⁴ even in those children undergoing invasive dental procedures while receiving a bisphosphonate,¹⁵ the long-term impact of these drugs on growing bones is uncertain.¹⁶ Likewise, although bisphosphonates may exert anti-tumor effects,^{17,18} minor hematological abnormalities have been described with the administration of these agents¹⁹ and longer term adverse sequelae on hematopoiesis should be considered, including relapsed disease. Consequently, we have undertaken studies of the short and long-term efficacy and safety of bisphosphonates in children with ALL.

Patients and Methods

Between January, 2000 and April, 2015 a total of 223 children and adolescents were diagnosed with ALL at McMaster Children's Hospital (MCH) in Hamilton, Canada. Six of them were infants, less than 12 months of age, who received very intensive chemotherapy according to Interfant protocols²⁰ and were excluded from this study. Among the 9 early deaths, 5 occurred during remission induction (2.3%) and one child was withdrawn from treatment by her family at the end of induction while another returned to his native country at the same juncture. The study sample of 217 were treated on regimens 00-001^{,21} 05-001²² and 11-001²³ of the Dana Farber Cancer Institute Childhood ALL Consortium in which MCH had been a member since 1985. These regimens were characterized by high cumulative doses of glucocorticosteroids and asparaginase. Details of their disease and clinical outcomes are given in Table 1. For the purposes of this report the study sample was followed until December 31, 2020.

It was our standard practice, in the time period 2000-2015, to undertake dual energy x-ray absorptiometry (DXA) on all children> 3 years of age at diagnosis and at intervals of 6 months thereafter for the duration of treatment; two years after remission induction²⁴. These examinations were performed with Hologic densitometers QDR 4500A and Discovery A (Hologic Inc., Waltham, MA). Each whole body scan results in radiation exposure of 20 microSv, less than $1/10^{\text{th}}$ of a chest x-ray.²⁵ Local normative data on body composition,²⁶ including bone mineral density (BMD),²⁷ were generated for 3-18 year olds and corrections for height, age and weight (HAW) were developed for BMD of the lumbar spine.²⁸

Children and adolescents with lumbar spine areal BMD (LS aBMD) Z scores of < -2.0 and those who were less osteopenic but had related bony morbidity, e.g. fractures, were candidates for treatment with a bisphosphonate, oral alendronate in all of them. Alendronate was administered weekly, in doses according to body weight (Table 2), to coincide with scheduled clinic attendance for chemotherapy, and all patients received daily supplemental calcium in the form of TUMS to provide 30 to 40mg/kg/d. Alendronate was administered while the children were fasting, as recommended.¹²

The study was approved by the Hamilton Integrated Research Ethics Board, project 3479 C.

Statistical analyses

Patient demographics including BMD were summarized using descriptive measures expressed as mean (standard deviation) or median (minimum, maximum) for continuous variables and number (percent) for categorical variables. Associations between categorical outcomes and clinical groups were assessed using Fisher's Exact test or chi-squared test. Impact of bisphosphonate therapy on BMD was tested using paired sample t test. The limit for statistical significance was set at two tailed $\alpha = 0.05$. Statistical software SPSS version 26 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) was used for analysis.

Results

Within the sample, the age range was 1 to 18 median 4 years (mean 5.7, SD 4.3) at the time of diagnosis and the M:F ratio was 116:101 (1.15). The majority had standard risk disease and almost 80% remain in continuous remission (Table 1). The interval from diagnosis to December 31, 2020 was 5.7 to 21.1 median 14.7 years (mean 14.5, SD 4.2).

The recipients of alendronate (n=69, 32%) were 1 to 18 median 6 years (mean 7.0 SD 5.2) of age at diagnosis and the M:F ratio was 37:32 (1.19). In the group who received alendronate 41% had high risk disease compared to 35% in the other group. Alendronate was administered for a mean (SD) of 87.1 (67.3) weeks; median 77, range 4 to 387 weeks. Two subjects were excluded from this analysis of duration of administration; one with Noonan syndrome received the drug for 6.5 years on the advice of an endocrinologist and another received prescriptions for 7.5 years but was felt to be largely non-compliant and had a LS aBMD Z score after this interval of -2.0. Both subjects were retained in the analysis of efficacy. LS aBMD prior to administration in the entire group of recipients is shown in Table 3.

SAFETY: Our experience with IV pamidronate in children with ALL has been reported.¹⁰ The side effects, including hyperpyrexia, were such that we abandoned the use of this agent. Alendronate was tolerated well overall and adherence was very high as a result of the schedule of administration. None of the participants experienced an acute phase reaction and only a few reported mild and short-lived gastrointestinal symptoms which did not interfere with compliance. However, one subject was truly intolerant, with symptomatic esophagitis, and so was withdrawn from further analyses.

Among those who received a course of alendronate, 7/68 (10.3%) relapsed, none during chemotherapy, of whom two died compared to 19/89 (21.3%), four during post-induction chemotherapy with four deaths, in those who did not receive the drug and were not lost to follow up. The difference in relapse rates is not statistically significant (p=0.06). An additional child who received alendronate was diagnosed with ALL 16 years after the original diagnosis. The phenotype was demonstrably different from that of the primary disease and so the new disease was deemed to be a second cancer, recognizing that this is a rare event.^{29,30}

EFFICACY

The interval from completion of the course of alendronate to the next DXA examination was a mean (SD) of 100.5 (86.5) weeks; median 79, range -30 to 465 weeks. One subject's last DXA was 6 months before finishing alendronate. The LS aBMD following alendronate is shown in Table 3 and represents a statistically significant increase, whether expressed as Z score (mean gain 1.31, p<0.0001) or HAW corrected Z score (mean gain 0.90, p<0.0001). While most of the subjects - 44/68 (65%) – still had negative Z scores, the majority (85%) gained BMD and 50/68 (74%) were within the normal range of -1.0 to +1.0. The correlation between duration of alendronate administration and the size of the gain in BMD was not statistically significant (r=0.017, p=0.891, nor was the correlation between the interval from completion of alendronate to next DXA examination and the size of the gain in BMD (r=-0.122, p=0.327).

A subgroup of 32 subjects had further DXA examinations, as part of their long term follow up, 5-9 years after finishing alendronate. Twenty-two of them (69%) still had negative Z scores although only half of those were osteopenic (LS aBMD Z score < -1.00). The results of the sequential DXA examinations on this subgroup are shown in Table 4 and Figure 1. The gains in BMD between time points 1 and 2 and between time points 1 and 3 were highly statistically significant (p<0.0001), but there was no significant difference in BMD between time points 2 and 3 (p=0.090). There was no relationship of Z scores or changes in Z scores to age or sex. Nine subjects had further scans more than 10 years from diagnosis as part of a cross-sectional study of long-term survivors; 8 had higher BMD Z scores than prior to receiving alendronate and only one was still osteopenic with a score of -1.6.

Discussion

Bisphosphonates are manifestly effective in the treatment of osteoporosis in adults by inhibiting osteoclastmediated bone resorption. Experience in children with low bone mineral is less extensive but generally supports the same conclusion.¹⁹ This is exemplified by a report on a small number (n=22) of children with a variety of chronic illnesses associated with loss of bone mineral, none with malignant disease.³¹ In a randomized clinical trial (RCT) the participants received either oral alendronate weekly or placebo for one year. Volumetric bone density of the lumbar spine increased significantly in the experimental group but not in those receiving placebo. Likewise, the cross-sectional moment of inertia per unit length of the femoral shaft - an estimate of mechanical strength - increased significantly only in the experimental group.³¹

A recent report from the Cincinatti Children's Hospital Medical Center is of a 7 year retrospective chart review describing the outcomes of intravenous bisphosphonate infusions in patients less than 21 years of age.³² Among the patients who were excluded were all of those (N=12) who had received cancer chemotherapy, but 29 of the study sample (N=123) were categorized as having glucocorticoid-induced osteoporosis. In the 42 patients who had at least two DXA examinations available for comparison there was a significant gain in LS aBMD) at one year after bisphosphonate infusion.

In the non-randomized study reported here, involving only children with ALL (n=68) on active therapy who received oral alendronate weekly for a shorter time than in the RCT reported by Rudge et al.,³¹ LS aBMD increased significantly as measured by Z score with and without HAW correction. The sequential results from DXA examinations are indicative of a short-term gain in LS aBMD from the administration of alendronate, blunting an otherwise downward trajectory. These changes occurred at an age when bone mass is increasing in healthy children, adolescents and young adults. In a population of healthy Caucasian subjects in Ohio, who were studied serially by DXA between the ages of 8-30 years,³³ the rate of accumulation of bone mass began to slow in mid to late teens in females (N=343) with peak BMD attained in the early 20s, while in males (N=312) the corresponding rate began to slow in late teens to early 20s with peak BMD attained by mid to late 20s. Comparable Canadian data have been reported.³⁴ Achieving a normal peak bone mass by age 30 is important in the prevention of osteoporosis in older adult life.³⁵ Consequently, rendering the subjects in this study osteopenic from the treatment of ALL, despite a temporary and only partial reprieve by the administration of alendronate, has put them at risk of fragility fractures in later life. In a separate study from our centre,³⁶ LS aBMD during maintenance/continuation therapy of ALL was shown to be predictive of later fractures in children who did not receive a bisphosphonate. The results in the small number of subjects (n=9) reported here, who were studied more than a decade after diagnosis, are intriguing, being suggestive of late improvement in LS aBMD, but longitudinal examination of a larger cohort will be required to evaluate this observation. A recent Dutch-Canadian collaborative study has demonstrated the predictive value of age and weight at diagnosis in relation to LS aBMD and to subsequent development of symptomatic fractures in children with ALL,³⁷ complementing our established practice of HAW correction of Z scores for aBMD of the lumbar spine.²⁸

The results of bone morphometry and measures of bone strength, determined by peripheral quantitative computed tomography $(pQCT)^{38}$ in our study of long term survivors of ALL (more than 10 years from diagnosis), have been reported separately.³⁹ There were no statistically significant differences in any of 19 metrics between those who had received bisphosphonate (n=14, pamidronate in 5) and those who had not (n=58). This may represent adaptive restructuring of trabecular bone by thickening of a reduced number of trabeculae to maintain bone strength.⁴⁰ Again, the improvement in LS aBMD following discontinuation of long-term steroid therapy has been reported in young adults with sarcoidosis.⁴¹

There have been few prior studies of bone by pQCT in children with ALL. Brennan et al. in the UK reported on 53 survivors on average almost 5 years after completion of treatment which did not include cranial radiation.⁴² There was no deficit in LS aBMD but reduced BMD in the trabecular bone of the distal radius was revealed. More recently, a group of 50 survivors in the US were studied within two years of completing treatment without cranial radiation, and again one year later.⁴³ A large group of healthy subjects afforded the provision of Z scores. Initial deficits were shown in both trabecular and cortical BMD in the

tibia. Subsequent changes in the cortical outcomes varied by the duration of the interval since completion of therapy. Interestingly, there were no associations of the outcomes with leukemia risk category, total glucocorticoid dose or antimetabolite therapy.

With respect to the short-term safety of oral alendronate, this has been assessed in detail in randomized clinical trials conducted in young people. In a study of 32 adolescents with anorexia nervosa who received the drug or placebo daily for one year, the authors stated "We found alendronate to be well tolerated and safe".⁴⁴ A more recent trial in 139 children with osteogenesis imperfecta, involving daily oral alendronate for two years, prompted the authors' observation "Importantly, ALN was associated with few adverse events. In particular gastrointestinal symptoms were not more common in patients receiving ALN than in those receiving placebo".⁴⁵ In a systematic review of bisphosphonates in children and adolescents with secondary osteoporosis Ward and colleagues noted that oral alendronate appeared to be well tolerated for intervals up to 3 years.⁴⁶ A report of the use of oral alendronate in post-menopausal osteoporosis stated that the drug was efficacious and well tolerated over a 10 year period.⁴⁷ In our non-randomized study gastrointestinal symptoms were infrequent and minor in degree, with one exception, and no other adverse sequelae were recorded. The retrospective study by Nasomyont and colleagues³² determined that "In 468 patient years of bisphosphonate exposure there were no reports of ONJ (osteonecrosis of the jaw) or AFF (atypical femoral fracture) in medical record." In a systematic review published in 2020 no cases of ONJ in children were identified.⁴⁸

The other safety issue addressed in our study is that of the relationship of bisphosphonates to the risk of cancer, in this instance relapse of ALL. We are not aware of this having been studied previously in children. By contrast, it has been a topic of considerable interest in the context of adults. Pre-clinical data and some, but not all, clinical trials suggest an anti-neoplastic effect of bisphosphonates.⁴⁹ A recent study using murine models of ALL showed a significantly shorter survival in animals receiving zoledronic acid, a third generation bisphosphonate, as well as chemotherapy compared to those receiving chemotherapy alone, but this was not seen using xenografts of human B precursor and T cell ALL.⁵⁰

A large study in the UK, using data extracted from the General Practice Research Database, examined 41,826 subjects who had been exposed to oral bisphosphonates and an equal number of matched controls,⁵¹ investigating the risk of developing cancer overall as well as specific neoplasms. It was reported that there was a significant protective effect in general and specifically in relation to breast and colorectal cancers. No such effect was evident for leukemias and lymphomas, but in no instance was the risk of cancer increased. In comparison, the results of a population-based cohort study in South Korea, using the National Health Insurance Services database, showed no association between exposure to oral alendronate or residronate and the risk of breast, ovarian or cervical cancer.⁵² This study involved 14,847 users and 204,525 unmatched controls.

A systematic literature review of the prognostic effect of bisphosphonate exposure in adult patients with a solid tumor found improved overall survival as well as cancer-specific and recurrence-free survival.⁵³ For individual cancer types there was an apparent benefit in overall survival for patients with gastro-esophageal cancer and longer cancer-specific survival in those with breast cancer. In a separate study, exposure to alendronate was associated with a lower risk of bone metastases in osteoporotic women with breast cancer.⁵⁴

Against this background our finding that there was no increased frequency of relapse in children receiving oral alendronate while undergoing active therapy for ALL may offer a measure of reassurance. Whether there was a protective effect is intriguing – the proportion of patients who relapsed after receiving alendronate was less than 50% of that in those who did not receive the drug, and more patients who received alendronate had high risk disease - but cannot be addressed with confidence. However, in a recent report,⁵⁵ B cell ALL cells were shown to mediate resorption of trabecular bone by a RANK-RANKL (receptor activator of nuclear factor kB ligand) mechanism through activation of osteoclasts. The authors postulated that combining an anti-resorptive agent with chemotherapy may reduce the risk of relapse by disrupting this B cell activity.

This was a retrospective cohort study with a small number of patients. Other limitations are the variability

in the duration of alendronate administration, although this reflects variation in the timing of responsiveness to this medication, and the lack of reliable information on fractures. A much larger longitudinal study with well-matched controls, perhaps in the form of a randomized trial to examine the efficacy of a bisphosphonate in osteopenic children with ALL, would be valuable.

Conflict of Interest statement. The authors have no conflicts of interest to declare

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Figure legend. Sequential lumbar spine bone mineral density Z scores in children and adolescents with acute lymphoblastic leukemia who received alendronate.

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Figure 1.



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TABLE 3.docx available at https://authorea.com/users/406883/articles/555620-safety-and-efficacy-of-alendronate-to-treat-osteopenia-in-children-during-therapy-for-acute-lymphoblastic-leukemia-a-retrospective-cohort-study-of-sequential-outcomes

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TABLE 4.docx available at https://authorea.com/users/406883/articles/555620-safety-andefficacy-of-alendronate-to-treat-osteopenia-in-children-during-therapy-for-acutelymphoblastic-leukemia-a-retrospective-cohort-study-of-sequential-outcomes