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Utriainen, Pauliina

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Short report:

Bisphosphonate treatment in children with acute lymphoblastic leukemia and osteonecrosis – Radiological and clinical findings in a national cohort

Authors: Pauliina Utriainen [1,2], Tuukka T Niinimäki [3], Anu J Huurre [4], Kaisa L Vepsäläinen [5], Outi M Mäkitie [1,2], Riitta A Niinimäki [6,7]

Children's Hospital and Pediatric Research Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland [1)]; Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland [2)]; Department of Surgery, Oulu University Hospital, Oulu, Finland [3)]; Department of Pediatric and Adolescent Medicine, Turku University Hospital, FICAN-West, and Turku University, Turku, Finland [4)]; Department of Pediatrics, Kuopio University Hospital and University of Kuopio, Kuopio, Finland [5)]; Department of Pediatrics and Adolescent Medicine, Oulu University Hospital and PEDEGO Unit, University of Oulu, Finland [6)]

Corresponding author:

Pauliina Utriainen
Department of Pediatric Hematology and Oncology
Children's Hospital and Pediatric Research Center, Helsinki University Hospital
Stenbäckinkatu 9, 00029 HUS, Helsinki, Finland
Pauliina.utriainen@hus.fi

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ABSTRACT

Osteonecrosis (ON) is a recognized complication of childhood ALL, but its optimal management remains unestablished. This study evaluated the effect of bisphosphonate (BP) treatment on evolution of ON lesions in childhood ALL.

We included a national cohort of ALL patients diagnosed with symptomatic ON before 18 years of age and treated with BPs (N=10; five males). Patients were followed both clinically and with serial MRIs. ON lesions were graded according to the Niinimäki classification.

The 10 patients had a total of 55 ON lesions. The median age was 13.3 years at ALL diagnosis and 14.8 years at ON diagnosis. Four patients had received HSCT before the ON diagnosis. BPs used were pamidronate (N=7), alendronate (N=2) and ibandronate (N=1). The duration of BP treatment varied between 4 months and 4 years. In 4/10 patients, BP treatment was given during the chemotherapy. BPs were well tolerated, with no severe complications or changes in kidney function. At the end of follow up 13/55 (24%) ON lesions were completely healed both clinically and radiographically; all these lesions were originally graded 3 or less. In contrast, ON lesions originally classified as grade 5 (joint destruction; N=4) remained at grade 5. All grade 5 hip joint lesions needed surgical treatment. During BP treatment, pain was relieved in 7/10 patients. At the end of follow up, none of the patients reported severe or frequent pain.

BP treatment was safe and seemed effective in relieving ON-induced pain in childhood ALL. After articular collapse (Grade 5) lesions did not improve with BP treatment. Randomized controlled studies are needed to further elucidate the role of BPs in childhood ALL-associated ON.

INTRODUCTION

Currently, more than 90% of children with acute lymphoblastic leukemia (ALL) can be cured (1). As cure rates improve, long-term sequelae have become of pivotal importance for the outcome of childhood ALL.

Osteonecrosis (ON) is a well-recognized complication in pediatric ALL (2). In its severe form, ON can lead to joint destruction and need of arthroplasty (3), but also milder forms cause pain and may warrant immobilization. Acknowledged risk factors for ON include high glucocorticoid dose, pubertal age, female gender, high body mass index, and hematopoietic stem cell transplantation (HSCT)(2, 4, 5, 6,7).

The optimal treatment of ON in pediatric ALL remains unestablished (5, 8, 9). Bisphosphonates (BPs), inhibitors of bone resorptive osteoclasts, are successfully used in children with congenital skeletal diseases such as osteogenesis imperfecta (10, 11). Thus far, little is known about BP treatment in children with ALL-related ON. In a retrospective study, treatment with zoledronic acid improved joint pain in majority of the pediatric ALL patients (12).

The location and extent have a great impact on the severity and prognosis of ON. Most previous classification methods have included only certain joints, making these methods suboptimal in pediatric ALL patients who typically present with widespread ON lesions (5). Recently, a radiological ON classification method including the entire skeleton was developed for pediatric and adult cancer patients (13, 14).

In this retrospective study, we describe the outcome of BP treatment in our national cohort of pediatric ALL patients with ON, also in respect to ON severity based on the established Niinimäki classification (13, 14).

PATIENTS AND METHODS

The inclusion criteria included ALL diagnosed between 1998-2013 at <18 years, symptomatic ON during or after (within 5 years of finalizing the treatment) leukemia treatment, and treatment with BPs. Patients were recruited from five tertiary centers, in which the treatment of childhood cancer has been centralized in Finland, by contacting the physicians in charge of patient care. Altogether 10 patients with a total of 55 ON lesions were identified and included in the study. ON diagnosis was based on symptoms: pain, limping, stiffness; no screening for ON was performed.

Data was retrospectively collected from hospital records. Patient records and MRI images were reviewed to confirm the inclusion criteria. ON was defined as a circumscribed lesion with a distinct rim of low signal intensity in the normally high-intensity bone marrow in T-1 weighted images (the band sign) and high intensity in the normally low-intensity bone marrow on short tau inversion recovery (STIR) images (double-line sign).

MRI images and the Niinimäki classification (13) were used for grading. ON lesions were evaluated independently by an orthopedic surgeon and a pediatric oncologist, blinded for patient data. If there was controversy between the two evaluating specialists that of the orthopedic surgeon was chosen.

STATISTICAL ANALYSES

Data analyses were performed using IBM SPSS statistical software for Windows, Version 26.0 (IBM Corp., Armank, NY, USA). The descriptive statistics are presented as median (range).

RESULTS

Cohort characteristics. The patient and treatment characteristics are shown in TABLE. The median ages at ALL and ON diagnosis were 13.3 years (range 2.0–17.7) and 14.8 years (2.8–20.8), respectively. Median ISO-BMI was 18.8 kg/cm^2 (16.7–26.3). Four patients had received HSCT prior to ON diagnosis. The median time from the primary ALL diagnosis to first ON lesion was 1.0 (0.0–10.3) years. The follow-up time from the first ON diagnosis was 5.7 (3.5–10.1) years.

BP treatment. Pamidronate was the most used BP (N=7 patients), followed by alendronate (n=2) and ibandronate (n=1)(TABLE). The duration of BP treatment varied (4 months-4 years), and the doses were individually tailored. The median time from ON diagnosis to the start of BP treatment was 0.33 years (-1.2–6.1 years). In one patient, BP treatment had been started for osteoporosis before the ON diagnosis. All patients had ON-related pain at the beginning of BP treatment. In 9/10 of the patients, the main indication for BP treatment was ON-related pain, while in one patient the indication was markedly wide-spread ON lesions (pat. 8, TABLE). In four patients, the BP treatment was given during chemotherapy.

All patients were supplemented with calcium during BP treatment. None of the patients showed severe adverse effects such as kidney failure or severe hypocalcemia. Three patients manifested mild, non-symptomatic hypocalcemia at the initiation of intravenous BP treatment. One patient reported bone pain and had fever after the second BP infusion. Parameters of kidney function were not affected in any of the patients.

ON lesions. On average, patients had 6 ON lesions (range 1–10), hip (n=10) and ankle (n=9) being the most common locations (FIGURE 1A). The median time from ALL

diagnosis to ON diagnosis (for the 55 ON lesions) was 1.0 years (range 0–10.3). At diagnosis, almost half (25/55) of the ON lesions were classified as grade 2, while 22 % (12/55) were graded 4 or 5 (FIGURE 1B.). In the four transplanted patients, 7/13 of the ON lesions were originally graded ≥4, while only 5/42 (12%) of the lesions were graded ≥4 in the non-transplanted patients (N=6). All patients with HSCT had an ON lesion graded 4 or 5 at diagnosis.

Evolution of the ON lesions by MRI. The changes in radiological grades of the ON lesions according to original grade are shown in FIGURE 1B-C. In the non-transplanted patients (N=6; 42 lesions), 28% of the ON lesions were totally healed, 45% had regressed, 43% were stable at last evaluation, and 12% had progressed to higher grades. Only 5 lesions were at grade 4 or 5. In contrast, half (54%) of the lesions in patients with HSCT were grade 5, and only 2 lesions were grade ≤2.

Orthopedic surgical treatment. Altogether 4/55 hip ON lesions (all originally graded ≥4) in three transplanted patients needed surgical treatment (TABLE). Average time from ON diagnosis to surgical operation was 2.7 (range 1.0–5.5) years.

Clinical outcome. During the BP treatment, pain was alleviated in 7/10 patients; in three patients (TABLE; patients 3,6,10) the pain symptoms totally disappeared within months into treatment. At the last follow-up visit, none of the patients reported continuous pain. Intermittent, mild pain was reported for 23 lesions (42%). (All patients with a surgery for hip joint deformation were pain free.) Restricted movements were reported in 39 (71%) of the lesions. All patients were at remission from their leukemia.

DISCUSSION

This is the first study to analyze the evolution of ON lesions using uniform classification method and serial MRIs in pediatric ALL children treated with BP:s.

MRI is the most accurate method for diagnosing ON. The Niinimäki classification (13) was developed for child and adult cancer patients, who typically have wide-spread ON lesions. This classification system includes all ON lesions, while most previous classification methods only included a certain joint (mainly hip or knee). Moreover, many previous studies have not used any classification method for ON. Using a uniform classification method enabled both the radiographic follow up of each ON lesion and comparison between individuals.

Our present cohort included only pediatric ALL patients who had developed symptomatic ON and were treated with BPs. The median age at leukemia and ON diagnosis in this small cohort are well in line with previous studies of ON incidence in childhood ALL, showing highest incidence in teenagers (6, 15, 16). Sex distribution was equal. These indicate that the decision to use BPs was not sex or age dependent. Also the time from ALL diagnosis to ON diagnosis (median 1 year) was similar as in previous descriptive study on ON in Nordic child ALL population (6).

In our cohort, ON-related pain was relieved in most of the patients during the BP treatment, in some within months. Although we cannot evaluate the role of spontaneous healing, this is in line with another rather small study showing beneficial effect on ON-related pain with zoledronic acid treatment in most of their pediatric ALL patients (12). Relieving the ON-related pain is important for the quality of life and for minimizing unnecessary pain medication use.

A complete clinical and radiographic healing was seen in almost one fourth of the ON lesions, all originally graded ≤3. Moreover, in non-tranplanted patients, most lesions were grade 2 or less at last imaging. As contrast, all ON lesions originally graded 5, indicating deformation of the joint, remained at grade 5. Three patients presenting originally with grade ≥4 lesion at hip later needed an operation for hip joint deformation.

There are no controlled studies of the effect of BPs on radiographic or clinical evolution of ON in childhood ALL. A recent article reviewed the previous five studies on BP treatment in pediatric ALL patients with ON (17). Almost half of the patients in the combined cohort showed progressive joint destruction despite BP therapy.

There are surprisingly few studies on the natural evolution of symptomatic ON in pediatric ALL. In a retrospective analysis of CCG-1882 protocol for ALL, ON-related pain or immobility were defined chronic in 84%, and 24% had undergone an orthopedic procedure (18). Radiographic changes were not reported. In another study, approximately 50% of the ON lesions remained stable, 25% regressed and 20% progressed (15). In comparison, none of our BP treated patients reported continuous pain at the end of follow up. Almost 90% of ON lesions were stable or regressive in the non-transplanted patients.

A previous study by our study group used the same classification method to assess the natural evolution of ON lesions in child and adult patients with cancer. In that study, 22% of the ON lesions needed surgical operation, including almost all hip ONs (33/36) and 16% of knee ONs. Only 2/26 hip ON lesions graded ≥3 healed completely (19).

There are multiple differences between these cohorts and our present study cohort, and they are thus not directly comparable.

It is to be noted that four patients developed ON after HSCT. The pathomechanisms in the transplanted patients probably differ somewhat from those of the other ALL-ON patients, which can affect the healing of these lesions. The main risk factor for the development of ON after HSCT is the glucocorticoid treatment needed to treat GVHD, although the evidence remains scarce and have been questioned (20, 21). Half of our transplanted patients had received glucocorticoids for GVHD before the ON diagnosis. Notably, ON was diagnosed late, even several years after HSCT, which may reflect a diagnostic delay in this subgroup. Indeed, all our transplanted patients had originally at least one ON lesion graded ≥4.

In some of our patients, BP treatment was started as long as 6 years after the ON diagnosis. One could assume that if BP treatment is postponed for too long, the metabolic window in which BPs could improve the healing process of ON lesion(s), might be lost.

BP treatment was well tolerated. None of our patients presented with serious side effects. Importantly, even the transplanted patients and those treated during front-line, multi-agent chemotherapy, tolerated the BPs well, with no kidney toxicity in any of our patients.

The main weakness of this study is the lack of a control group. It is impossible to determine the independent role of BPs in the healing of ON lesions, since also spontaneous healing occurs in pediatric ALL patients. We acknowledge that our study cohort is small although it includes all BP treated ALL-ON patients in our country. The

advantage of our study is the careful follow up both clinically and with serial MRI images, analyzed by same two trained physicians for this study.

Early diagnosis of ON is important, to provide time for interventions before the progression to joint collapse. When considered indicated, the BP treatment should probably be given soon after ON diagnosis. BPs can be used during chemotherapy, provided that renal function is normal. If ON lesion(s) involve a weight-bearing joint (grade 5) at first MRI evaluation, BPs do not seem beneficial, unless indicated for pain management.

In summary, BP treatment seems safe and effective in relieving ON-related pain in childhood ALL. Randomized controlled studies are needed to evaluate the effect of BPs on the healing process of ON in ALL.

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TABLE 1. Patient and treatment characteristics of the pediatric patients with pre-B-ALL and osteonecrosis treated with bisphosphonates (N=10).

Pat.	Diagnosis	Sex	Age at leukemia dg	Treatment protocol	HSCT (+/-) GVHD (+/-)	Age at ON dg	No of ON lesions	Highest ON grade at dg	BP treatment; duration	BP treatment; timing	Surgery	Pain
1	Pre-B-ALL ;secondary AML	Male	5.8	NOPHO-ALL 1992 HR + NOPHO-AML	HSCT +; twice No GVHD nor glucocorticoids after 2. HSCT	16.1 (3yr5mo after 2. HSCT)	6	4	Pamidronate iv; Duration 2.3 yrs	After treatment	Yes; Hip arthroplasty	Pain was significantly relieved after 1 year of BP treatment
2	Pre-B-ALL	Male	14.8	NOPHO-ALL 1992 HR	HSCT + GVHD + needing glucocorticoids for 7 months	16.9 (16 months after HSCT)	2	5	Pamidronate iv; 0.3 yrs (2 doses)	After treatment	-	No clear effect on pain
3	Pre-B-ALL	Female	5.1	NOPHO-ALL 2008 SR	-	5.8	1	2	Pamidronate iv; 1.8 yrs	During leukemia treatment; at first maintenance (1 year into treatment)	-	Pain was relieved within 2 months after the first BP infusion

4	Pre-B-ALL	Male	14.5	NOPHO-ALL 1992 IR & NOPHO-ALL 2000 HR (relapse)	HSCT +; after relapse; GVHD needing glucocorticoids for 4 months	20.8 (25 months after HSCT)	2	5	Pamidronate iv; 1.4 yrs, then alendronate po for 2 years	After treatment	Yes; Hip arthroplasty (operation planned before BP treatment)	Hip joint operation soon after BP start – the effect of BP cannot be evaluated Pain in other joints ameliorated during the 2. year into BP treatment
5	Pre-B-ALL	Female	17.7	NOPHO-ALL 2008 SR	-	18.2	6	4	Alendronate po; 4.1 yrs	During leukemia treatment; after 10 months into leukemia treatment), at maintenance 1	-	Pain was significantly relieved after appr. 1.5 years of BP treatment
6	Pre-B-ALL	Female	14.0	NOPHO-ALL 2008 SR -> HR	-	14.0 (At diagnosis)	9	4	Alendronate po; 3.6 yrs	During ALL treatment;from induction through the whole	-	Pain disappeared btw 3 and 9 months after BP start

										leukemia treatment		
7	Pre-B-ALL	Male	13.9	NOPHO-ALL 2008 SR	HSCT + No GVHD nor glucocorticoids	15.6 (11 months after HSCT)	2	5	Ibandronate po; 1.3 yrs	After treatment	Yes; Hip osteotomy	No clear effect on pain
8	Pre-B-ALL	Male	7.8	NOPHO-ALL 2008 SR	-	8.9	7	5	Pamidronate iv; 1.8 yrs	After completing ALL treatment	-	Pain was only mild at beginning of BPs despite wide-spread, progressive lesions -> No pain after BP start
9	Pre-B-ALL	Female	2.0	NOPHO-ALL 2008 SR	-	2.8	10	3	Pamidronate iv; 1.8 yrs	After completing ALL treatment	-	Pain was ameliorated within 5 months of BP treatment, but mild, intermittent pain symptoms continued
10	Pre-B-ALL	Female	12.6	NOPHO-ALL 2008 SR	-	12.9	9	3	Pamidronate iv; 1.0 yrs	During the ALL treatment; at final po	-	Originally severe pain was significantly relieved after 6 months of BP treatment, and

										maintenance		totally disappeared later

ON, osteonecrosis; HSCT; hematopoietic stem cell transplantation; GVHD, graft versus host disease; BP, bisphophonate

FIGURE 1

A. Distribution of osteonecrosis (ON) lesions (N=55) in 10 pediatric ALL patients treated with bisphosphonates.

B. Evolution of the 55 ON lesions with follow-up. Classification grades 1 to 5 according to Niinimäki classification*. At the last evaluation, 80% (N=44) of the ON lesions were either regressed to lower stages or were stable, while 20 % of the lesions had progressed. Altogether 13 ON lesions (24 %) had totally healed. None of the ON lesions that were originally graded 4 or 5 were totally healed. All lesions originally graded as 5 (deformation of joint) remained at grade 5 at the last evaluation.

C. Evolution of ON lesions a) at hip (N=10) and b) at knee (N=8) c) at ankle (N=8) and d) shoulder (N=7) according to original grading.

*The Niinimäki classification, grades 1 to 5, is based on the following characteristics of the ON lesions: location (weight-bearing or non-weight bearing bone; long or short bone; diaphysis-metaphysis-epiphysis), the area of articular surface involvement and deformation of the joint (ref. 13; FIGURE 2, supplemented).