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Efficacy of pamidronate in pediatric osteosarcoma patients with low bone mineral density

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Purpose: Most surviving pediatric osteosarcoma patients experience osteoporosis, bone pain, and pathologic fracture during and after therapy. The aim of this study was to evaluate the efficacy and side effects of pamidronate therapy in these patients.

Methods: Nine osteosarcoma patients (12.8±1.6 years of age; 5 boys and 4 girls) who had a history of nontraumatic fracture or severe pain after completing chemotherapy were included. Intravenous pamidronate (1.5 mg/kg) was given every 6 weeks for 4 to 6 cycles. Bone mineral density (BMD) of the lumbar spine was measured by dual-energy x-ray absorptiometry. Clinical outcomes including acute side effects were also evaluated.

Results: After pamidronate treatments, all patients experienced decreased pain. Seven of 9 patients could walk without a crutch. The BMD of lumbar spine was increased by 0.108±0.062 mg/cm^2 after 8.4±1.0 months (n=8, *P*=0.017) and the mean *z*-score improved from −2.14±0.94 to −1.76±0.95 (*P*=0.161). Six patients (67%) had an acute-phase reaction, and 2 patients had symptomatic hypocalcemia.

Conclusion: Pamidronate appears to be safe and effective for the treatment of osteosarcoma in children with low BMD and bone pain.

Keywords: Child, Osteosarcoma, Pamidronate, Bone mineral density

Introduction

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents. The introduction of preoperative neoadjuvant chemotherapy has improved the survival and limb-salvage rate in osteosarcoma patients by decreasing the tumor burden before surgery[1]. However, a high prevalence of osteoporosis and a high fracture rate were reported in long-term surviving osteosarcoma patients, especially in the affected limbs[2,3]. Furthermore, most of the patients' bone mineral density (BMD) decreased during treatment including tumor resection and chemotherapy[4]. Decreased physical activity along with poor nutrition during treatment might impair bone mass gain[2,3]. Furthermore, chemotherapy agents such as methotrexate (MTX) are associated with bone pain, osteoporosis, and nontraumatic fractures[5].

The bisphosphonates such as pamidronate (3-amino-1-hydroxypropylidene-bisphosphonate) have been shown to decrease the risk of skeletal fractures and bone pain in adults with metastatic breast cancer and multiple myeloma[6,7]. Pamidronate is also used as a successful treatment for osteoporosis caused by osteogenesis imperfecta, quadriplegic cerebral palsy, congenital neutropenia, and leukemia without any drug-related complications in children[8,9]. Furthermore, pamidronate is known to be a potent inhibitor of human osteosarcoma cell growth *in vitro*[10]. Recently, another bisphosphonate, zoledronate, was shown to be effective in regression of osteosarcoma and repression of lung metastases *in vivo*[11].

The aim of this study was to evaluate the efficacy and safety of pamidronate in children with osteosarcoma who had low BMD or fracture after chemotherapy.

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Materials and methods

1. Patients

This study was a retrospective chart review of 9 osteosarcoma patients who were treated with pamidronate from March 2003 to March 2006 at the Korea Cancer Center Hospital. Pamidronate was administered to osteosarcoma patients with severe bone pain requiring continuous pain control including narcotics or a pathologic fracture.

2. Dual–energy x–ray absorptiometry measurements

We initially evaluated their lumbar spine and both ankles through simple radiographs and then confirmed by dual energy x-ray absorptiometry (DXA). Low BMD, a surrogate marker of osteoporosis in pediatrics, was defined by *z*-scores below –2.0 based on Korean pediatric reference data[12]. The BMDs of the lumbar spine (BMD_{LS}) were measured before and after pamidronate treatment using a Lunar Prodigy Advance DXA bone densitometer (GE Lunar Corp., Madison, WI, USA) with pediatric software (enCore 2005 ver. 9.15.010; GE Lunar Corp.).

3. Pamidronate treatment

Pamidronate was administered after obtaining written informed consent. Pamidronate was administered daily for 3 consecutive days, and this 3-day dosing session was repeated at 6-week intervals for at least 6 months (total of 4–6 dosing sessions). For each treatment session, 0.5-mg pamidronate/kg with 400 mL of 0.9% saline was infused intravenously for over 4 hours. To ensure uniformly adequate calcium and vitamin D intake, all participants were taking Cal-D-Vita 1,500 mg; Roche (elemental calcium 600 mg and 400 IU vitamin D) daily.

For safety, we checked for signs of hypocalcemia or other acute adverse effects of bisphosphonate at each hospital visit, and had all the patients and their parents to acknowledge the signs and symptoms. A blood sample was obtained at the start of each 3-day dosing session. After the first dose of pamidronate, ionized calcium was measured. Additional samples were obtained at the end of each 3-day session before discharge. Routinely, total calcium, phosphate, alkaline phosphatase, blood urea nitrogen, creatinine, electrolyte, magnesium, and parathyroid hormone (PTH) levels were checked by our hospital laboratory. When patients complained of hypocalcemic symptoms, additional ionized calcium, PTH, and magnesium were measured.

4. Statistical analysis

The data are presented as means±standard deviations. The net BMD_{LS} or BMD_{LS} *z*-scores between before and after pamidronate therapy were assessed using a Wilcoxon signed rank test. *P* values <0.05 were considered statistically significant. Analyses were carried out using SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA).

Results

1. Patient characteristics

The baseline characteristics of the subjects are summarized in Table 1. There were 5 boys and 4 girls with an average age of 12.8±1.6 years (range, 10.2–15.2 years). The mean duration of the off-therapy interval before pamidronate therapy was 9.5 months (range 1–36 months). Seven patients underwent 4 dosing sessions, and 2 underwent 6 sessions. All patients had stage IIB osteosarcoma according to the American Joint Committee on Cancer staging. The primary sarcomas were at knee joint region (distal femur, 5; proximal tibia, 2; proximal fibula, 2). All patients were unable to walk owing to the bone pain, and 5 patients had previous fractures.

2. Clinical outcome

A marked reduction in bone pain was noted 2 to 6 weeks after the first pamidronate session, with only an occasional recurrence of mild pain before the next session. After completion of the pamidronate sessions within 6 months, 7 patients could walk without a crutch and no longer needed painkillers.

Table 1. Characteristics of the patients with osteosarcoma

Patient	Sex	Age (yr)	Tanner stage	AJCC staging	Location	No. of previous fractures	BMD_{LS} *z*-score[a]	Other
1	M	13.0	III	IIB	Femur, distal	0	–1.35	
2	M	14.8	III	IIB	Tibia, prox	1	–3.21	Could not walk for 3 years
3	M	15.2	V	IIB	Femur, distal	1	–1.45	
4	F	11.3	III	IIB	Femur, distal	1	–3.89	Local recurrence
5	F	11.8	II	IIB	Fibula, prox	0	–1.90	
6	F	10.2	I	IIB	Femur, distal	0	–2.28	Wound infection
7	M	12.3	II	IIB	Femur, distal	0	–1.72	
8	F	13.7	V	IIB	Fibula, prox	1	–1.31	Foot drop
9	M	13.8	III	IIB	Tibia, prox	2	–2.42	

AJCC, American Joint Committee on Cancer; BMD_{LS}, bone mineral density lumbar spine; prox, proximal.
[a]At start of chemotherapy.

One patient (case 6) could not walk owing to a local infection, and another patient (case 4) had severe osteoporosis as she had chemotherapy for 3 years owing to local recurrence. Two patients (cases 3 and 4) had nontraumatic fractures (case 3, left femur; case 4, right femur) after cessation of the pamidronate therapy. Fracture healing was not delayed, and there was no instance of fracture nonunion.

3. Changes in BMD

The interval between BMD evaluations was 8.4±1.0 months in 8 patients (24 months in case 1). Initially, the BMD_{LS} *z*-scores were −2.14±0.94 (range, −1.31 to −3.21). After treatment, the mean BMD_{LS} increased by 0.108±0.062 mg/cm^2 (*P*=0.017), and the mean *z*-score improved from −2.14±0.94 to −1.76±0.95 (*P*=0.161) (Fig. 1). The BMD_{LS} *z*-scores of case 9 improved from and −2.42 to −0.77 by 24 months (BMD_{LS} increased from 0.717 to 1.001 mg/cm^2). Further, the BMD_{LS} *z*-score of case 1 improved from −1.35 to 0.88 (BMD_{LS} increased from 0.69 to 0.87 mg/cm^2).

4. Side effects and complications

Six of 9 patients had an elevated body temperature over 38.5℃ (axillary). They also complained of bone pain in the back and limbs during the first 3-day-dosing session. However, no recurrent symptoms occurred in subsequent sessions. Two patients had symptomatic hypocalcemia (cases 2 and 4). During the first session, 2 patients had perioral numbness with decreased ionized calcium, low magnesium, and increased PTH levels, which resolved with additional oral calcium and magnesium supplementation. Before each subsequent session and after the last session, the calcium and phosphate levels of all patients were within the normal range.

Discussion

This is the first report of BMD changes in pediatric osteosarcoma patients with pamidronate therapy. We found that pamidronate therapy is effective and safe for increasing BMD and controlling bone pain.

In long-term survivors of childhood limb sarcoma such as osteosarcoma or Ewing's sarcoma, the prevalence of osteopenia or osteoporosis was reported as 28.3% to 65.0%[2,13,14]. We also reported that 47.5% of long-term survivors of osteosarcoma had osteoporosis and 30.0% had osteopenia at the age of 22.0±5.1 years[3]. Furthermore, most of the patients' BMD decreased during treatment[4]. One cause of osteopenia or osteoporosis is the toxicity of MTX in adjuvant chemotherapy. In particular, high-dose MTX is known to cause osteopathy with bone pain, osteoporosis, and increased risk of fracture[15]. Another cause might be impaired acquisition of appropriate peak bone mass (PBM) in children with limb sarcoma. During puberty, bone mass accumulates rapidly to reach PBM through adequate exercise and nutritional support[16]. However, most children with osteosarcoma are diagnosed during early to midadolescence[1]. Thus, they fail to reach PBM. Subjects who fail to achieve optimal PBM and strength during childhood and adolescence are more likely to develop osteoporosis later in life[17].

The use of bisphosphonate therapy in pediatric patients was first suggested in 1998. Cyclic administration of intravenous pamidronate in children with osteogenesis imperfecta resulted in reduced bone resorption, increased BMD, relief of bone pain, and reduced fracture incidence[18]. Furthermore, efficacy of bisphosphonate treatment was proven in other pediatric diseases including juvenile idiopathic osteoporosis, steroid-induced osteoporosis, quadriplegic cerebral palsy, and juvenile rheumatoid arthritis[19-21]. Our study also supports the effect of pamidronate in increasing BMD and relief of bone pain in osteosarcoma patients with osteoporosis, although a reduction in fracture incidence could not be ascertained owing to the limited number of cases. Most patients in this study did not use analgesics and could walk with weight bearing in the affected limb after the pamidronate treatment. In acute lymphoblastic leukemia patients with steroid-associated osteonecrosis, pamidronate appeared to be effective in reducing bone pain[22]. Recently, Meyers et al.[23] reported pamidronate improved the durability of limb reconstruction without impairing the efficacy of chemotherapy in osteosarcoma patients.

In this study, 67% of patients had an acute-phase reaction (influenza-like symptoms), and 22% had symptomatic hypocal-

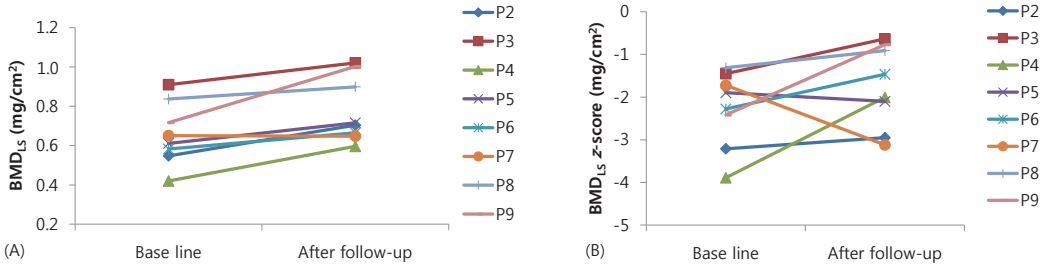

Fig. 1. The lumbar spine bone mineral density changes after pamidronate treatment. (A) Changes in bone mineral density lumbar spine (BMD_{LS} mg/cm^2) of osteosarcoma patients (P2 to P9, case 2 to 9) at baseline and after follow-up. (B) Changes in the BMD_{LS} *z*-scores of osteosarcoma patients. The interval from first BMD_{LS} evaluation to next BMD_{LS} evaluation was 8.4±1.0 months.

cemia. This result is compatible with other bisphosphonate studies of pediatric patients[18,24-27]. An acute-phase reaction including fever, malaise, nausea, diarrhea, and muscle or bone pain occurs in most children with the initiation of intravenous or oral agents. These symptoms began typically within 1–3 days of initial exposure, lasted only a few days, and rarely recurred with subsequent doses. Abnormal laboratory findings including hypocalcemia and hypophosphatemia, which were less common and typically had no symptoms, resolved within several days[27]. Our patients with hypocalcemia also had hypomagnesemia. We assume the other chemotherapy regimen, cisplatin, induces hypomagnesemia through its renal toxicity[28]. Magnesium deficiency is known to contribute to hypocalcemia[29]. Thus, a correction of magnesium deficiency before pamidronate therapy is essential along with adequate vitamin D and calcium intake in osteosarcoma patients. Until now, the 3-year safety and efficacy data of bisphosphonate use in children for secondary osteoporosis were considered sufficient in a 2007 Cochrane review[30].

We acknowledge some limitations in our study. First, selection bias may exist because of the retrospective chart review of only 9 osteosarcoma patients. Second, the small number of patients without controls precludes a definite conclusion regarding the effectiveness of pamidronate on BMD. Finally, the changes in femur neck BMD might be more related to walking ability. However, we could not measure femur neck BMD serially for safety and technical reasons.

In conclusion, we found that pamidronate therapy is safe and effective in increasing BMD and controlling bone pain in children and adolescents with osteosarcoma and low BMD with or without fracture. However, the small number of cases precludes a definitive conclusion on whether pamidronate therapy is effective in preventing fracture. Further longitudinal studies with larger samples are needed.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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