HHS Public Access

Author manuscript

Am J Hosp Palliat Care. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Am J Hosp Palliat Care. 2019 February ; 36(2): 138–142. doi:10.1177/1049909118793114.

Bisphosphonate use in pediatric oncology for pain management

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Abstract

The use of bisphosphonates for pain control in children with cancer is not extensively studied. We retrospectively evaluated 35 children with cancer treated with intravenous bisphosphonates for pain management at a single institution from 1998 through 2015. We analyzed pain scores and opioid and adjuvant medication consumption before bisphosphonate administration, daily for 2 weeks and at 3 and 4 week after administration. We also determined the time interval between diagnosis and first administration of bisphosphonates and duration of life after bisphosphonate administration. Mean pain scores were 2.45 (± 2.96) and 0.75 (± 1.69) before and 14 days after bisphosphonate administration, respectively ($P = 0.25$), and morphine equivalent dose of opioids were 5.52 (± 13.35) and 5.27 (± 9.77), respectively ($P = 0.07$). Opioid consumption was significantly decreased at Days 4–8, 11–12, and Week 3 after first bisphosphonate administration. The median duration of life after first bisphosphonate administration was 80 days, indicating its use late in the course of treatment.

Bisphosphonates did not significantly improve pain outcomes at 2 weeks, but opioid consumption was reduced at several time points during the first 3 weeks. The use of bisphosphonates earlier in the course of pediatric oncological disease should be evaluated in prospective investigations.

Keywords

bisphosphonate; pain management; pediatric cancer; opioid consumption; pain scores; adjuvant pain medication

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to report.

INTRODUCTION

Recent advances in cancer-directed therapy have substantially improved the overall survival rate of childhood cancer.[1] However, the outcomes of children with solid tumors, especially bone metastases, remain poor.[1] In general, strategies for pain management in pediatric oncology are based on escalation of treatment options from non-opioid to opioid medications for nociceptive pain and the use of adjuvant classes of medications for neuropathic pain including gabapentinoids and tricyclic antidepressants. Children with bone cancers frequently experience extreme pain and require increased palliative care, which may entail the administration of high doses of opioids. Because pain control is an important aspect of therapy for these patients, the development of an appropriate pain management plan is crucial.

Bisphosphonates (BPs) are structurally similar to inorganic pyrophosphate, with a carbon atom at the center of the two phosphonate groups.[2] The mechanism of action of BPs occurs primarily through binding to hydroxyapatite crystals on bone surfaces, resulting in their internalization within osteoclasts. This binding functionally impairs osteoclasts by inhibiting the biochemical pathways necessary for bone resorption.[2] Nitrogen-containing BPs (e.g., zoledronate, pamidronate, and alendronate) are more potent osteoclast inhibitors than are non–nitrogen-containing BPs (e.g., etidronate and clodronate), and zoledronate is the most potent of BPs.[2] Nitrogen-containing BPs impair osteoclast function by interfering with the mevalonate pathway, causing cytoskeletal defects, whereas non-nitrogenous BPs disrupt ATP production. Additionally, the secondary effect of all BPs is a decrease in the number of mature osteoclasts through apoptosis.[3]

As inhibitors of osteoclasts, BPs limit bone resorption and reduce the pain associated with the breaking down of bone tissue. Intravenously administered BPs reduce the risk of skeletal complications and alleviate pain in adult patients with metastatic cancer.[4,5] Because BPs protect skeletal integrity and produce acute analgesic effects in bony conditions lacking the etiology of osteolytic or inflammatory responses, BPs are recommended to control chronic pain caused by bone metastases.[6]

The side effects of BPs include electrolyte disturbances, flu-like symptoms, nausea, and less commonly but more seriously—osteonecrosis of the jaw and renal dysfunction.[12,13] Electrolyte abnormalities, specifically hypocalcemia and hypophosphatemia, are common. Therefore, inpatient monitoring is recommended for 3 to 4 days post infusion, and calcium supplementation (with or without vitamin D) should be considered.[12,14]

Although pamidronate and zoledronate are frequently used to reduce skeletal complications and treat bone pain in adults with metastatic bone disease,[8–10] few studies have reported the use of BPs in children with cancer.[1,11] In one study, two pediatric patients with acute lymphoblastic leukemia (ALL) and pain received pamidronate for vertebral fractures.[11] In another study, a retrospective analysis of a series of case reports revealed that zoledronate was used in 19 pediatric patients with metastatic cancer.[1] Despite the limited use of BPs in children, BP therapy may improve pain control and mobility and prevent fractures in children with low bone mineral density caused by cancer or cancer-directed therapy.[11] In

addition, BPs may improve bone strength and pain control in children with metastatic disease in one or more bone sites.[1]

Here, we review our institutional experience with the use of intravenous BPs in children with cancer, for the indication of pain control. We used a pain outcome methodology that we verified in a previous study of pain outcomes in pediatric oncology.[15]

METHODS

This study was approved by the institutional review board. We evaluated the use of intravenous BPs at a single pediatric oncology academic research institution treating children, adolescents and young adults, from September 1998 to November 2015, for the indication of reducing pain related to cancer. Patients treated for other indications such as hypercalcemia, fracture, or osteopenia/osteoporosis or patients who received oral BPs were excluded from this analysis.

We collected the following data: (i) patient characteristics—including age, sex, race/ethnicity, and disease diagnosis; (ii) drug characteristics—including BP type, dosing information, number of administrations, and the time interval between administrations; (iii) pain outcomes—including pain intensity and pain medication (opioid or adjuvant medications) consumption; and (iv) the duration of disease progression before and after BP administration—including the duration of life after the initiation of BP therapy and the time from diagnosis to BP administration. If a patient received more than one dose of BPs, the pain intensity and pain medication data pertaining to only the first BP dose were evaluated. Pain intensity was calculated as the mean value of all available daily pain scores for each patient.

Pain assessment was standardized with age-appropriate tools: the Face, Legs, Activity, Cry, Consolability scale[16] for children younger than 4 years; the Wong-Baker FACES scale[17] for patients 4 to 7 years old; and the numerical pain scale[18] for patients older than 7 years; all scales are 11 points scales from 0 to 10. Pain medication data included opioids and all adjuvant medications for the treatment of pain. Opioid medications data included oral opioids and intravenous opioids (either as patient-controlled analgesia or intermittent, as-needed doses). For analysis, all opioid doses were converted to intravenous morphine equivalent doses (mg/kg per day) by opioid equianalgesic potency. The following potency ratios were used: fentanyl:morphine, 100:1; hydromorphone:morphine, 5:1; and oral codeine:morphine, 1:12. The adjuvant pain medications in the categories of gabapentinoids and tricyclic antidepressants were noted, and the doses were analyzed.

Pain outcome measures were collected before and after BP administration as follows: within 14 days before BP administration (Day –1), the day of BP administration (Day 0), daily post administration for the first 2 weeks (Day 1–14), at 3 and 4 weeks post administration (Week 3 and Week 4). The duration of life after initiating BP therapy was calculated from the first day of BP treatment to the last day of life. The duration of time between the date of diagnosis and the first dose of BP was also calculated.

Descriptive statistics were computed for the patients' characteristics at baseline and after BP administration. The differences in pain score distribution between baseline and follow-up time points were examined using Wilcoxon signed rank test for the paired and ordinal data, and the P values were then adjusted for multiplicity using the false discovery rate method.[27] Kaplan-Meier estimators were calculated for time to death and time to BP administration for patients with neuroblastoma or non-neuroblastoma cancer diagnoses. These times were tested with Wilcoxon rank sum test, as no censoring was observed among all patients. A correlation analysis was also performed to determine the relation between duration of life and time without BP administration.

RESULTS

Patient characteristics

During the study period, 35 patients received intravenous BP treatment for the indication of pain reduction and had evaluable pain outcome data. The patient characteristics are presented in Table 1. The most prevalent diagnosis was neuroblastoma with bone metastases (23 patients, 66%). The majority of patients were younger than 13 years (29 patients, 83%), with a median age of 9.2 years (range, 3.1–20.4). All patients in this study died as a result of their oncological diagnoses.

Bisphosphonate therapy

Thirty-five patients received 58 doses of BPs intravenously, including 55 doses of zolendronic acid and 3 doses of pamidronate, and were included in the analyses. Zoledronate was administered to the majority of patients (33 of 35, 94.3%), with a mean of 1.68 doses per patient, administered at a mean of 47 days between doses, at a mean dose of 2 mg/m^2. Two patients received pamidronate and zoledronate in subsequent doses.

Pain outcomes

For all pain outcome measures (i.e., pain scores and opioid or adjuvant medication consumption), data pertaining to the first BP dose were analyzed (Table 1).

Mean pain scores were 2.45 (± 2.96) and 0.75 (± 1.69) before and 14 days after bisphosphonate administration, respectively ($P = 0.25$), and morphine equivalent dose of opioids were 5.52 (± 13.35) and 5.27 (± 9.77), respectively ($P = 0.07$). Opioid consumption was significantly decreased at Days 4–8, 11–12, and Week 3 after first bisphosphonate administration. Bisphosphonates did not appear to significantly improve pain outcomes at 2 weeks, but opioid consumption was reduced at several time points during the first 3 weeks.

Six patients received adjuvant gabapentin for pain, which was administered at a median dose of 1,350 mg/day (range, 100–3,600 mg/day) at Day –1 and at 2,700 mg/day (range, 900–3,600 mg/day) at Week 4. Two patients received adjuvant amitriptyline, which was administered at a dose of 25 mg per day at Day –1 and at a median dose of 37.5 mg per day (range, 25–50 mg/day) at Week 4.

Duration of disease before and after initiation of BP therapy

We analyzed the relative time points of the first BP dose during the treatment course in relation to their date of diagnosis and date of death, respectively. The median time from the first BP dose to the time of death was 80 days, and the median time from diagnosis to the first BP dose was 805 days. For patients with neuroblastoma (the most prevalent diagnosis in our study), the median time from their first BP dose to death was 80 days, and the time from diagnosis to their first BP dose was 936 days. All patients included in this study died of their disease.

DISCUSSION

Currently, BPs have been reported in the treatment of solid tumors with bone involvement,[1,12,19] ALL,[11,20,21] and Langerhans cell histiocytosis.[22] However, the number of reports describing the use of BPs for treating children with cancer is limited, especially when pain is the outcome measured.

In the relatively few studies that have investigated BP administration in children, BPs were well tolerated, transiently arrested endochondral ossification, improved bone mineralization, decreased the risk of vertebral fractures, and provided acute pain control.[1,2,11,20–22] Although the sample sizes in these studies were relatively small and measurements of pain outcomes were not standardized, these findings, nevertheless, suggest that BPs are clinically beneficial as a treatment for pain in pediatric patients with bone cancer.

Here, we investigated pain outcomes with a design focused on pain intensity, opioid consumption as morphine equivalent dose per day, and the use of adjuvant medications for pain. Additionally, we evaluated the timing of BP treatment in relation with the times of diagnosis and death. Neuroblastoma with bone metastases was the most frequent cancer type in our study, and patients younger than 13 years composed the most prevalent age group. The predominance of neuroblastoma with bone metastases in our study, as opposed to primary bone tumors such as osteosarcoma and Ewing sarcoma, may be due to the higher prevalence of neuroblastoma in the general pediatric population.[23]

We evaluated intravenous administration of BPs because this route is associated with high potency and advantageous dose-response, including pamidronate and zoledronate. The dosing used in our study (≤ 4 mg/m^2) is consistent with previous reports of the use of BPs in children with no major adverse effects, including renal dysfunction or osteonecrosis of the jaw.[13,19] The current zolendronate dosing recommendation at our institution is 2.3 mg/m^2, with a time interval of at least 4 weeks between doses for the indication of bone pain related to metastases.

The lack of statistically significant differences in pain intensity scores after BPs administration may have multifactorial implications. We observed a fluctuating pattern of pain intensity and opioid consumption over the 4 weeks after BP administration. In general, pain intensity appeared to be mild to moderate in the group when evaluated as a whole. This may reflect dynamic changes in pain treatment options, including escalation of treatment with multiple medications. Because pain management medication data have not been

reported in any previous studies of BP administration in children, we were unable to compare our results with those of other studies. Nevertheless, the opioid consumption observed in our study was generally high, with a maximum of 178 mg/kg per day morphine equivalent dose. This aggressive opioid treatment may have overpowered any observable analgesic effects of BP. However, it is more likely that the BPs appeared to be ineffective because of the limited duration of life of the patients, as BPs were administered late in the course of disease and close to the end of life.

The limited duration of life observed in our study reflects the general indication of the use of BPs as a late option in the armamentarium of pain management. Indeed, BPs are usually only considered after traditional pharmacologic options for pain management (e.g., opioids or adjuvant medications, such as gabapentin, amitriptyline, or methadone) have been exhausted.[1,8,13] Others have recommended that BPs should be used as an earlier intervention.[20] In a Phase I study of zoledronate and low dose cyclophosphamide in recurrent/refractory neuroblastoma in pediatric patients, the median overall survival was 12.3 months.[19] This is considerably longer than the median overall survival observed in our study.

Among the limitations of this study, one must consider the retrospective design and the inclusion of time points when subjects were outpatients, which limited the availability of pain score and opioid consumption data. Additionally, we did not evaluate a number of variables that could have influenced pain outcomes and possibly the course of disease, including the use of radiation therapy, steroids and nonsteroidal anti-inflammatory drugs, specific chemotherapy (e.g., palliative chemotherapy for pain control), and psychological support for teaching nonpharmacological interventions for pain.

In summary, the use of BPs for pain indications in children did not appear to affect pain intensity with statistical significance, while the opioid consumption was decreased at several time points after administration of BPs. The consumption of high doses of opioids observed in our study may have masked a more modest analgesic effect of BPs. Our observation that BPs were given late in the course of life is notable. Several reports have demonstrated a tumor suppressive role of BPs, especially zoledronate, in primary and secondary adult bone cancers.[24–26] We recommend the investigation of the use of bisphosphonates earlier in the course of pediatric oncological disease, in prospective investigations.

ACKNOWLEDGEMENTS

We thank Nisha Badders, PhD, ELS, for the scientific editing of this manuscript.

This study was supported by the National Cancer Institute Cancer Center Support Core Grant 5P25CA023944 and ALSAC, neither of which had a role in its planning, conduct, analysis, or reporting.

Abbreviations:

ALL	acute lymphoblastic leukemia
BP	bisphosphonate

REFERENCES

1. August KJ, Dalton A, Katzenstein HM, et al. The use of zoledronic acid in pediatric cancer patients. Pediatr Blood Cancer, 2011;56: 610–614. [PubMed: 21298747]
2. Battaglia S, Dumoucel S, Chesneau J, et al. Impact of oncopediatric dosing regimen of zoledronic acid on bone growth: preclinical studies and case report of an osteosarcoma pediatric patient. J Bone Miner Res, 2011;26: 2439–2451. [PubMed: 21713986]
3. Hughes DE, Wright KR, Uy HL, et al. Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. J Bone Miner Res, 1995;10: 1478–1487. [PubMed: 8686503]
4. Lteif AN, Zimmerman D. Bisphosphonates for treatment of childhood hypercalcemia. Pediatrics, 1998;102: 990–993. [PubMed: 9755274]
5. Lipton A Bisphosphonate therapy in the oncology setting. Expert Opin Emerg Drugs, 2003;8: 469–488. [PubMed: 14662000]
6. Bonabello A, Galmozzi MR, Bruzzese T, et al. Analgesic effect of bisphosphonates in mice. Pain, 2001;91: 269–275. [PubMed: 11275384]
7. Berenson J, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. N Engl J Med, 1996;334: 488–493. [PubMed: 8559201]
8. Hortobagyi G, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med, 1996;335: 1785–1791. [PubMed: 8965890]
9. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst, 2002;94: 1458–1468. [PubMed: 12359855]
10. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic Acid Versus Placebo in the Treatment of Skeletal Metastases in Patients With Lung Cancer and Other Solid Tumors: A Phase III, Double-Blind, Randomized Trial—The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. J Clin Oncol, 2003;21: 3150–3157. [PubMed: 12915606]
11. Goldbloom EB, Cummings EA, Yhap M. Osteoporosis at presentation of childhood ALL: management with pamidronate. Pediatr Hematol Oncol, 2005;22: 543–550. [PubMed: 16166046]
12. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int, 2008;74: 1385–1393. [PubMed: 18685574]
13. Goldsby R, Fan TM, Villaluna D, et al. Feasibility and dose discovery analysis of zoledronic acid with concurrent chemotherapy in the treatment of newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group. Eur J Cancer, 2013;49: 2384–91. [PubMed: 23664013]
14. Bamias A, Kastritis E, Moulopoulos LA, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol, 2005;23: 85808587.
15. Anghelescu D, Goldberg JL, Faughnan LG, et al. Comparison of pain outcomes between two anti-GD2 antibodies in patients with neuroblastoma. Pediatr Blood Cancer, 2015;62: 224–228. [PubMed: 25382742]
16. Merkel SI, Voepel-Lewis T, Shayevitz JR, et al. The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediatr Nurs, 1997;23: 293–297. [PubMed: 9220806]
17. Hockenberry MJ, Wilson D. Wong's Essentials of Pediatric Nursing. 9th ed St Louis, MO: Elsevier Mosby;2013.
18. von Baeyer CL, Spagrud LJ, McCormick JC, et al. Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. Pain, 2009;143: 223–227. [PubMed: 19359097]
19. Russell HV, Groshen SG, Ara T, et al. A phase I study of zoledronic acid and low-dose cyclophosphamide in recurrent/refractory neuroblastoma: a new approaches to neuroblastoma therapy (NANT) study. Pediatr Blood Cancer, 2011;57: 275–282. [PubMed: 21671363]
20. Alos N, Grant RM, Ramsay T, et al. High Incidence of Vertebral Fractures in Children With Acute Lymphoblastic Leukemia 12 Months After the Initiation of Therapy. J Clin Oncol, 2012;30: 2760–2767. [PubMed: 22734031]

21. Phillips B Towards evidence based medicine for paediatricians. Arch Dis Child, 2016;101: 772.
22. Chellapandian D, Makras P, Kaltsas G, et al. Bisphosphonates in Langerhans cell histiocytosis: an international retrospective case series. Mediterr J Hematol Infect Dis, 2016;doi: 10.4084/MJHID.2016.033.
23. Cohn SL, Pearson AD, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol, 2009;27: 289–297. [PubMed: 19047291]
24. Green JR, Clezardin P. Mechanisms of bisphosphonate effects on osteoclasts, tumor cell growth, and metastasis. Am J Clin Oncol, 2002;25: S3–9. [PubMed: 12562045]
25. Green JR. Antitumor effects of bisphosphonates. Cancer, 2003;97: 840–847. [PubMed: 12548584]
26. Dickson PV, Hamner JB, Cauthen LA, et al. Efficacy of zoledronate against neuroblastoma. Surgery, 2006;140: 227–235. [PubMed: 16904974]
27. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society Series B (Methodological), 1995;57(1): 289–300.

Table 1:

Characteristics of Patients Treated with Intravenous Bisphosphonates for Cancer Related Pain (n=35)

Characteristic	Number of Patients (%)
No. of patients (%)	**N=35 (100)**
Age	
Median (min, max)	9.2 (3.1, 20.4)
<13 years	29 (82.9)
≥13 years	6 (17.1)
Sex	
Male	18 (51.4)
Female	17 (48.6)
Race	
White	16 (45.7)
Other	19 (54.3)
Status	
Expired	35 (100)
Alive	0
Diagnosis	
Neuroblastoma with bone metastases	23 (65.7)
Ewings sarcoma	7 (20)
Osteosarcoma	3 (8.6)
Other*	2 (5.7)

*One patient each with the diagnosis of medulloblastoma and chondrosarcoma

Table 2:

Pain Scores and Opioid Consumption (IV Morphine Equivalent Doses, MED) for 35 Patients Treated with IV Bisphosphonate

Days	Pain Scores (PS) Mean (SD) Median (range)	Number of Patients with PS data*	Raw P Wilcoxon paired	Bonferroni adjusted P	MED (mg/kg/day) Mean (SD) Median (range)	Number of Patients with MED data**	Raw P Wilcoxon paired	Bonferroni adjusted P
Day −1 or 0 *	2.5 (3)	24			5.5 (13.4)	34		
Day 1	2.2 (2.5)	21	0.65	1	3.3 (4.7)	30	0.17	1
Day 2	1.6 (2.5)	18	0.30	1	4.4 (8.4)	29	0.38	1
Day 3	2.1 (3.3)	20	0.29	1	4.6 (7.5)	31	0.10	1
Day 4	2.3 (2.5)	16	0.50	1	5.3 (7.5)	29	0.012	0.2
Day 5	1.8 (3)	17	0.27	1	4.5 (5.7)	31	0.030	0.5
Day 6	1.8 (2.6)	17	0.06	0.9	12.5 (34.5)	27	0.040	0.6
Day 7	1.6 (2.5)	12	0.16	1	6.7 (9.6)	27	0.022	0.4
Day 8	2 (3.3)	11	0.08	1	8.5 (14.4)	25	0.034	0.6
Day 9	1.6 (2.2)	10	0.09	1	8.3 (20.1)	24	0.08	1
Day 10	0.4 (1.1)	8	0.25	1	6.2 (9.9)	24	0.09	1
Day 11	1.5 (1.8)	11	0.17	1	6.1 (10.1)	24	0.012	0.2
Day 12	1.7 (2.5)	9	0.31	1	4.4 (8.3)	23	0.041	0.7
Day 13	1.9 (3.5)	10	0.84	1	4.2 (7.4)	22	0.11	1
Day 14	0.8 (1.7)	10	0.25	1	5.3 (9.8)	20	0.07	1
Week 3	2 (2.7)	19	0.31	1	5.6 (10.5)	22	0.024	0.4
Week 4	1.9 (2.4)	18	0.01	0.2	7 (12.8)	18	0.20	1

*Day −1 was used as reference group in paired Wilcoxon test for pain score and day 0 for Opioid use.

**Number of patients contributing data for each specific data point (for day −1 and 0, the highest number of patients who contributed to data for either one of the time points