Int J Clin Exp Med 2020;13(7):5092-5099
www.ijcem.com /ISSN:1940-5901/IJCEM0111172

Original Article

Loading-dose ibandronate improves opioid-resistant headache in locoregionally advanced nasopharyngeal carcinoma patients prior to concurrent chemoradiotherapy

Bingguang Chen[1*], Hanwen Huang[1*], Bang Cai[1], Peng Zhao[1], Jiaxing Su[1], Mingji Yan[1], Ge Wen[2]

[1]*Department of Oncology, Yunfu People's Hospital, Yunfu 527300, Guangdong, China;* [2]*Department of Radiation Oncology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou 510150, Guangdong, China.* [*]*Equal contributors.*

Received March 20, 2020; Accepted May 20, 2020; Epub July 15, 2020; Published July 30, 2020

Abstract: A considerable proportion of patients with nasopharyngeal carcinoma (NPC) suffer from opioid-resistant headaches due to tumor bone invasion and are often undertreated. Therefore, effective treatment is essential for these patients. Twenty-three patients were included in this study and treated with loading-dose ibandronate (6 mg infused over 30 minutes on 3 consecutive days). The headache severity was reduced within 3-7 days (mean: 4.0 ± 1.3 days) in these patients. Relative to the baseline, on days 3, 7, and 14, the pain scores were lower (6.3 ± 1.4 versus 4.7 ± 2.6, 3.0 ± 1.7, 2.6 ± 1.5, respectively; $P<0.001$) and the analgesic usage was reduced (393.0 ± 50.7 mg vs. 339.1 ± 48.1 mg, 243.5 ± 74.3 mg, 177.4 ± 84.3 mg, respectively; $P<0.001$) in the treated patients. These patients did not exhibit hepatic or renal toxicity, and the treatment was well-tolerated. Therefore, this loading-dose ibandronate regimen appears to be a safe and efficacious means of relieving opioid-resistant headaches in NPC patients with bone invasion.

Keywords: Bisphosphonates, ibandronate, pain, nasopharyngeal carcinoma, opioid-resistant

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most frequently-identified forms of head and neck cancer among patients in southern China [1]. NPC patients commonly (53-65%) suffer from headaches that arise due to tumor bone invasion at the skull base and/or the intracranial tissue [2, 3]. The patients with locally advanced NPC often undergo curative concurrent chemoradiotherapy, which is sufficient to relieve their headache symptoms [4, 5]. Between the initial diagnosis and the radiotherapy initiation, however, there is typically a relatively long period during which time the patient's pain is often insufficiently managed. Serious headaches can dramatically reduce the quality of life in these patients and can also reduce their confidence in anti-cancer treatments such that pain relief can improve this confidence [6]. Approximately 20% of NPC patients with bone involvement suffer headaches that cannot be relieved by systemic analgesics, resulting in severe pain in these individuals [7, 8]. As such, it is essential that a novel means of treating opioid-resistant headaches be established to treat NPC patients suffering from this condition.

Tumor-directed osteoclastic bone resorption and the associated neurological injuries are the primary tumor-associated causes of bone pain in cancer patients [9]. Bone cancer-related pain is often treated using bisphosphonates as part of an adjuvant therapeutic regimen, and these drugs have been found to mediate analgesic activity in this context as they can bolster bone mineral density and can suppress bone resorption [10]. The third-generation bisphosphonate ibandronate has been found to be capable of alleviating bone pain, reducing skeletal event incidences, and improving patient quality of life

in individuals with tumor bone metastases [11]. A loading-dose ibandronate regimen (i.v. 6 mg administered daily for 3 consecutive days) has been shown to be effective as a means of quickly alleviating moderate-to-severe metastatic bone pain, even when this pain is resistant to opioid treatment [12-15]. Such treatments can be more readily employed as ibandronate does not exhibit the cumulative dose-limiting nephrotoxicity induced by other bisphosphonates like zoledronate and pamidronate [16, 17]. Whether loading-dose ibandronate can be used to successfully treat moderate-to-severe opioid-resistant headaches in NPC patients suffering from skull base bone invasion, however, remains to be determined.

Given that there is prior evidence showing that loading-dose ibandronate therapy can effectively reduce metastatic bone pain, we designed the present pilot study as a means of evaluating the short-term efficacy and safety of such a therapeutic regimen in NPC patients exhibiting skull base bone invasion and suffering from moderate-to-severe opioid-resistant headaches.

Materials and methods

Patients

The present pilot study had a non-randomized open-label design. From April 2017 to June 2019, NPC patients meeting the following criteria were recruited: patients who had undergone no prior treatment; patients who had T3-4 stage disease of any N stage; patients who suffered moderate-to-severe headaches (pain score ≥4) that could not be adequately controlled using opioid analgesics. We excluded all the NPC patients exhibiting distant metastases and/or renal or hepatic abnormalities. Our institutional ethics committee approved this study.

Prior to the treatment, all the patients were subjected to a complete physical examination, and a full medical history was taken. In addition, serum biochemistry and hematological analyses were conducted, as was a biopsy of the primary tumor, a nasopharyngeal fiberoptic endoscopy, and nasopharyngeal magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) analysis (with the former only being conducted when MRIs were contraindicated). Bone scans, liver ultrasounds, and X-ray or CT-based chest imaging were also conducted. In order to minimize the potential for osteonecrosis or osteomyelitis, dental evaluations were also conducted in these patients. Tumor staging was based upon the American Joint Committee on Cancer (AJCC) TNM Staging System for the Nasopharynx (8th ed., 2017).

Treatment

All the patients in the present study had undergone treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics. The initial opioid doses were 5 mg every 4 hours for immediate release morphine, and titration was performed to optimize the pain control [18]. As soon as the diagnoses and staging of the patients were confirmed, they were treated with three cycles of induction chemotherapy plus concurrent chemoradiotherapy.

Patient headaches were evaluated immediately after their initial visit and on day 7 after the initiation of the analgesic treatment. Those headaches which caused consistent pain even after the opioid dose-escalation or treatment with the maximum tolerable dose of multiple opioids were considered to be opioid-resistant [14]. Patients with opioid-resistant headaches received an intravenous loading-dose ibandronate (AIMOKUN®; Chengdu Easton Biopharmaceuticals Co., Ltd., Chengdu, China) infusion, and treatment with ibandronate (6 mg in 250 mL 0.9% NaCl daily for >30 minutes on 3 consecutive days) was performed as described in previous studies [13, 19]. During the treatment, the opioid analgesic treatment was maintained, with dosages being adjusted as appropriate. No changes were made in the antineoplastic regimens.

Assessments

A visual analog scale (VAS) was used to assess headache severity, with scores ranging from 0 (no pain) to 10 (worst pain possible). Baseline assessments of both the VAS pain scores and the opioid utilization were made on day 7 post-initiation of the analgesic treatment. Thereafter, the VAS scores were recorded daily while the pain evaluations were conducted on days 3, 7, and 14 following the initiation of loading-dose ibandronate treatment. Opioid intake was measured daily and was converted into an oral morphine equivalent daily dose (MEDD) index (in mg) to allow an easier comparison and analy-

Table 1. Baseline characteristics of the nasopharyngeal carcinoma patients (n = 23)

Characteristics	Number	Percentage (%)
Gender		
Male	16	69.6
Female	7	30.4
Karnofsky performance status score		
90-100	20	87.0
70-80	3	13.0
Histology		
Keratinizing	2	8.7
Non-keratinizing	21	91.3
Tumor (T) category*		
T3	15	65.2
T4	8	34.8
Lymph node (N) category*		
N1	9	39.1
N2	10	43.5
N3	4	17.4
Disease stage*		
III	14	60.9
IVA	9	39.1
Painful area		
Frontal	10	43.5
Parietal	7	30.4
Temporal	6	26.1
Pain score		
4-6	13	56.5
7-9	10	43.5

*According to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system.

sis. The MEDD was calculated as the daily intake of opioids multiplied by the relative potency ratio, which is 3:1 for parenteral to oral morphine, 1.5:1 for oral oxycodone to oral morphine, and 100:1 for transdermal fentanyl to oral morphine [20, 21].

The pain responses were evaluated based on the changes in the pain scores and opioid utilization relative to the baseline. A complete pain response was one in which the patient pain scores were reduced to 0 and opioid consumption was decreased or stable, while the partial responses were those for which the pain scores were decreased by at least one point, or for which the pain scores were unchanged but opioid utilization was reduced by at least 25%. Pain progression was defined as cases for which the pain scores rose by at least one point, or the opioid consumption increased by at least 25%. If the pain scores and opioid utilization remained unchanged, the pain was considered to be stable [22].

The efficacy was assessed based on the changes in the opioid utilization and the pain scores following loading-dose ibandronate treatment relative to baseline. The safety of this therapeutic regimen was assessed based on hematological examinations, tests of renal and hepatic functionality (including measurements of serum creatinine and transaminase), and the identification of any adverse events. Laboratory testing was conducted at baseline and on days 7 and 14, while the toxicity was graded based upon the National Cancer Institute Common Toxicity Criteria v 5.0.

Statistical analysis

SPSS v. 22.0 (IBM, IL, USA) was used for the statistical analysis. The data were compared using Student's *t*-tests and are shown as the means ± standard deviation (SD). $P<0.05$ was the significance threshold.

Results

Patient characteristics

In total, we included 23 patients in the present study. This patient population had a median age of 43 years (range: 36-64 years). The headache locations were described as frontal, parietal, and temporal. The patients reported accompanying symptoms including dizziness (8 patients), aural fullness/tinnitus (7 patients), nasal congestion (4 patients), facial numbness (5 patients), blurred vision or diplopia (3 patients), and ptosis (1 patient). Of these patients, three had a family history of nasopharyngeal carcinoma. For full details regarding the patients' baseline characteristics, see **Table 1**.

Pain scores and analgesic consumption decreased after loading-dose ibandronate treatment

At baseline, these patients had a mean pain score of 6.3 ± 1.4. This score was reduced to

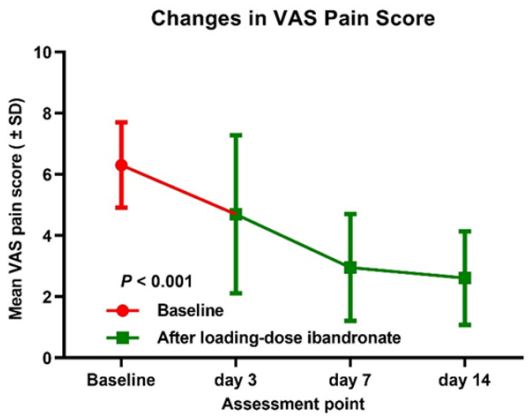

Figure 1. Mean visual analog scale (VAS) scores for the 23 patients over the course of the treatment with loading-dose intravenous ibandronate (6 mg for 3 consecutive days).

4.7 ± 2.6 on day 3 and was further decreased on days 7 and 14 (all $P<0.001$ relative to the baseline; **Figure 1**; **Table 2**). Consistent with these reduced pain scores, the opioid consumption fell significantly over time, with a mean baseline MEDD of 393.0 ± 50.7 mg that fell to 339.1 ± 48.1 mg on day 3 of treatment and was further reduced on days 7 and 14 (all $P<0.001$ vs. the baseline; **Figure 2**; **Table 2**). Thus, loading-dose ibandronate achieved a more rapid decrease in the pain scores and a significant reduction in MEDD.

The patients exhibited good responses to loading-dose ibandronate treatment

On day 3 of the treatment, 1/23 (4.3%) of the patients reported a complete pain response, 12/23 (52.2%) reported a partial response, and 10/23 (43.5%) reported stable pain. On day 7, 2/23 (8.7%) of the patients reported a complete pain response and 21/23 (91.3%) reported a partial response. On day 14 of the treatment, 3/23 (13.0%) and 20/23 (87.0%) of the patients reported complete and partial pain responses, respectively. No patients exhibited pain progression during the study period. Overall, these patients achieved satisfactory levels of headache relief within 7 days following the loading-dose ibandronate treatment, with a mean duration of 4.0 ± 1.3 days (range: 3-7 days).

Safety and tolerability of the loading-dose ibandronate treatment

The patients did not exhibit any significant treatment-related adverse events during the study period, and there were no instances of altered renal or hepatic functionality or changes in the hematological parameters in the treated patients (all $P>0.05$ vs. baseline; **Table 3**). Importantly, there were no instances of osteonecrosis of the jaw.

A total of 3 patients (13.0%) exhibited mild grade 1 flu-like symptoms such as fever, fatigue, or myalgia within three days of the initiation of the loading-dose ibandronate treatment. These symptoms returned to normal after 2-3 days without any intervention. A total of 7 patients (30.4%) suffered from grade 1 nausea that abated within 2-3 days without any intervention. No serious adverse events were detected. The loading dose of ibandronate was well tolerated, so it can be administered without any additional toxicity.

Discussion

In patients with locally advanced NPC, headaches most often result from tumor invasions of structures, including the clivus, the sphenoid sinus, the skull base, or the parapharyngeal soft tissue, with nerve involvement potentially contributing to or aggravating these symptoms. Cancer-associated bone pain has been shown to be particularly resistant to pain treatment [23]. Osteoclast-mediated osteolytic bone destruction has been shown to contribute to the incidence of bone cancer pain, and tumor- and stromal cell-derived growth factors and cytokines can further promote osteoclast activation [24].

Ibandronate is a nitrogen-containing bisphosphonate capable of inhibiting osteoclast-mediated bone resorption by strongly bonding to bone surface hydroxyapatite crystals that are preferentially internalized by osteoclasts. Once within these cells, it then induces apoptotic cell death through the inhibition of the key mevalonate pathway enzyme farnesyl pyrophosphate synthase [10, 11]. Owing to its ability to interfere with this mevalonate pathway, multiple preclinical trials have shown that ibandronate can inhibit the growth of different tumor cell lines, and it has also been found to synergize with docetaxel [25, 26]. Ibandronate can further inhibit inflammatory cytokine production, thereby ameliorating inflammatory edema and hyperalgesia in response to mechanical stimulation [27].

Table 2. Changes in the pain scores and opioid consumption following ibandronate treatment (mean ± SD)

Parameter	Baseline	3 days	7 days	14 days
Pain score	6.3 ± 1.4	4.7 ± 2.6	3.0 ± 1.7	2.6 ± 1.5
MEDD (mg/d)	393.0 ± 50.7	339.1 ± 48.1	243.5 ± 74.3	177.4 ± 84.3

MEDD: Morphine equivalent daily dose.

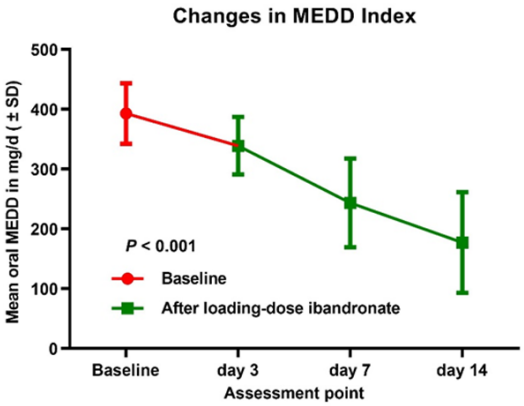

Figure 2. Mean oral morphine equivalent daily dose (MEDD) values for the 23 patients over the course of the treatment with loading-dose intravenous ibandronate (6 mg for 3 consecutive days).

A phase III randomized trial analyzing 466 metastatic breast cancer patients demonstrated that a standard dose ibandronate regimen (6 mg infused intravenously over 1-2 hours every 3-4 weeks) can relieve metastatic bone pain [28, 29]. In this study, the infusion of 6 mg of ibandronate mediated significantly improved pain relief relative to a placebo or to a bolus injection of 2 mg ibandronate, and this pain relief was sustained for as long as 2 years following treatment. While such standard ibandronate doses can thus alleviate metastatic bone pain, maximal pain relief may not be achieved for several weeks. However, other preclinical studies have found that nitrogen-containing bisphosphonates can induce osteoclast apoptosis in a dose-dependent manner [30, 31]. There have also been multiple randomized, open-label, multicenter studies demonstrating that an intravenous ibandronate dose of 6 mg administered over 15 minutes every 3-4 weeks is safe and does not induce any long term renal toxicity [32, 33].

Given its lack of significant renal toxicity, high doses of intravenous ibandronate can be safely administered to patients, thereby significantly improving the flexibility of treatment options for those with moderate-to-severe bone pain in need of rapid relief. Prior work has clearly demonstrated that a loading-dose ibandronate regimen can provide rapid and sustained relief to patients suffering from metastatic bone pain [12, 13]. For example, in one open-label, prospective, non-randomized study of 25 hormone-refractory prostate cancer patients with moderate-to-severe metastatic bone pain, short term ibandronate treatment (6 mg infused over 60 minutes on 3 consecutive days) was sufficient to achieve significant analgesia within an average of 3 days (range: 1-5 days) and without any renal toxicity [12]. A separate prospective, phase II, open-label study of 13 female breast cancer patients suffering from moderate-to-severe metastatic bone pain similarly found that loading-dose ibandronate therapy (6 mg infused over 15 minutes on 3 consecutive days) led to significant pain reductions in 8.2 ± 3.3 days. In these patients, the mean VAS scores fell from 6.1 ± 0.9 at baseline to 3.2 ± 2.2 on day 7 and 3.0 ± 2.1 on day 14 (all $P<0.01$ vs. baseline), and these reductions coincided with the mean MEDD reductions and a lack of renal toxicity or serious adverse events [13].

The management of opioid-resistant bone cancer pain remains challenging, and there is an urgent need for the development of drugs capable of providing rapid relief to patients. Our results suggest that loading dose ibandronate therapy may be one such effective intervention for these patients. In the present study, we were able to demonstrate that treatment with loading-dose ibandronate therapy (6 mg infused i.v. over 30 minutes on 3 consecutive days) was sufficient to reduce the pain scores in patients with moderate-to-severe opioid-resistant headaches arising due to NPC invasion of the skull base. The treated patients all exhibited some degree of headache relief within a seven-day period following the initial infusion, and this relief was sustained for the study duration. These patients also significantly reduced their analgesic drug consumption, further underscoring the value of providing patients with loading-dose ibandronate as an adjuvant co-analgesic therapy.

Table 3. Changes in the serum creatinine (Scr), alanine aminotransferase (ALT), and serum calcium following the ibandronate treatment (mean ± SD)

Parameter	Baseline	7 days	*t* value	*P** value	14 days	*t* value	*P** value
Scr (μmol/L)	54.48 ± 7.25	58.04 ± 7.38	1.664	0.110	54.13 ± 7.54	0.218	0.830
ALT (U/L)	29.83 ± 7.05	28.78 ± 7.86	0.465	0.647	28.87 ± 7.24	0.490	0.629
Serum calcium (mmol/L)	2.35 ± 0.10	2.32 ± 0.09	1.148	0.263	2.30 ± 0.10	1.563	0.132

**P* values versus baseline for all comparisons.

In previous trials, loading dose intravenous ibandronate therapy has been shown to be an effective means of quickly relieving opioid-resistant bone metastasis pain associated with a range of primary tumor types [14, 15]. For example, one open-label pilot study analyzed the outcomes in 18 such patients (VAS scores = 5-6; opioid-resistance = approximately 400 mg/d MEDD) and found that loading-dose ibandronate (4 mg infused over 120 minutes on 4 consecutive days) resulted in the patients achieving significant pain reductions within a seven-day period that remain significant on day 21 ($P<0.0001$) and day 42 ($P<0.05$) relative to baseline without any renal toxicity or increase in the mean MEDD [14]. A separate open, prospective, non-randomized study of 33 patients with opioid-resistant (400 mg/d MEDD) metastatic bone pain associated with different primary tumor types also found that loading-dose ibandronate (6 mg infused over 60 minutes on 3 consecutive days) was able to mediate a marked reduced bone pain within a 3-5 days period. For these patients, the mean VAS scores fell from 6.8 (range: 6-8) at baseline to 4.9 (range: 3-7) on day 3-5 and 3.7 (range: 2-7) on day 5-7 (all $P<0.01$ vs. baseline) without any increases in analgesic consumption or major adverse events [15].

The results of this trial highlight the tolerability of an intravenous loading-dose ibandronate regimen and underscore the safety of this treatment strategy. All treatment-related adverse events in this analysis were mild and abated without specific treatment within 2-3 days. Importantly, no patients exhibited jaw osteonecrosis, hepatic dysfunction, or renal deterioration. Consistent with this result, previous studies have not observed any significant acute nephrotoxicity following intravenous loading-dose ibandronate treatment [12-15], even in individuals exhibiting pre-existing impairments of renal functionality [34].

There are many limitations to the present analysis. For one, our study size was relatively small, the study duration was short, and there was no placebo group included in the analysis. Even so, we believe that this pilot trial highlights the feasibility and potential safety/efficacy of loading-dose ibandronate regimens, providing a valuable framework for future large, randomized controlled trials aimed at validating the findings of the present study.

In summary, our results suggest that a loading-dose ibandronate regimen can be used safely and effectively as an analgesic therapy in NPC patients with skull base bone invasion suffering from moderate-to-severe opioid-resistant headaches. As such, this may represent a novel therapeutic modality that is well-suited to relieving pain in these patients.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ge Wen, Department of Radiation Oncology, The Third Affiliated Hospital of Guangzhou Medical University, No. 63, Duobao Road, Liwan District, Guangzhou 510150, Guangdong, China. Tel: +86-020-81292789; E-mail: wenge@gzhmu.edu.cn

References

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-386.

[2] Wu ZX, Xiang L, Rong JF, He HL and Li D. Nasopharyngeal carcinoma with headaches as the main symptom: a potential diagnostic pitfall. J Cancer Res Ther 2016; 12: 209-214.

[3] Zhang SX, Han PH, Zhang GQ, Wang RH, Ge YB, Ren ZG, Li JS and Fu WH. Comparison of SPECT/CT, MRI and CT in diagnosis of skull base bone invasion in nasopharyngeal carci-

noma. Biomed Mater Eng 2014; 24: 1117-1124.
[4] Zhou R, Zhu J, Chen X, Liu Y, Wang Y and Zhang T. The efficacy and safety of docetaxel, cisplatin and fluorouracil (TPF)-based induction chemotherapy followed by concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: a meta-analysis. Clin Transl Oncol 2020; 22: 429-439.
[5] Lee YL and Ho CY. Headache as the sole symptom of nasopharyngeal carcinoma and its clinical implications. ScientificWorldJournal 2012; 2012: 143829.
[6] Wells NL and Sandlin V. Expectations of pain and accompanying symptoms during cancer treatment. Curr Pain Headache Rep 2012; 16: 292-299.
[7] Cleeland CS, Janjan NA, Scott CB, Seiferheld WF and Curran WJ. Cancer pain management by radiotherapists: a survey of radiation therapy oncology group physicians. Int J Radiat Oncol Biol Phys 2000; 47: 203-208.
[8] Yau V, Chow E, Davis L, Holden L, Schueller T and Danjoux C. Pain management in cancer patients with bone metastases remains a challenge. J Pain Symptom Manage 2004; 27: 1-3.
[9] Goblirsch MJ, Zwolak PP and Clohisy DR. Biology of bone cancer pain. Clin Cancer Res 2006; 12: 6231s-6235s.
[10] Ebetino FH, Hogan AM, Sun S, Tsoumpra MK, Duan X, Triffitt JT, Kwaasi AA, Dunford JE, Barnett BL, Oppermann U, Lundy MW, Boyde A, Kashemirov BA, McKenna CE and Russell RG. The relationship between the chemistry and biological activity of the bisphosphonates. Bone 2011; 49: 20-33.
[11] Bauss F and Bergstrom B. Preclinical and clinical efficacy of the bisphosphonate ibandronate in cancer treatment. Curr Clin Pharmacol 2008; 3: 1-10.
[12] Heidenreich A, Elert A and Hofmann R. Ibandronate in the treatment of prostate cancer associated painful osseous metastases. Prostate Cancer Prostatic Dis 2002; 5: 231-235.
[13] Altundag K, Dizdar O, Ozsaran Z, Ozkok S, Saip P, Eralp Y, Komurcu S, Kuzhan O, Ozguroglu M and Karahoca M. Phase II study of loading-dose ibandronate treatment in patients with breast cancer and bone metastases suffering from moderate to severe pain. Onkologie 2012; 35: 254-258.
[14] Mancini I, Dumon JC and Body JJ. Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. J Clin Oncol 2004; 22: 3587-3592.
[15] Maier GS, Eberhardt C and Kurth AA. Ibandronate: the loading dose concept in the treatment of metastatic bone pain. J Bone Oncol 2016; 5: 1-4.
[16] Bergner R, Diel IJ, Henrich D, Hoffmann M and Uppenkamp M. Differences in nephrotoxicity of intravenous bisphosphonates for the treatment of malignancy-related bone disease. Onkologie 2006; 29: 534-540.
[17] Jackson GH. Renal safety of ibandronate. Oncologist 2005; 10 Suppl 1: 14-18.
[18] Scarborough BM and Smith CB. Optimal pain management for patients with cancer in the modern era. CA Cancer J Clin 2018; 68: 182-196.
[19] Wang R, Zhang S, Jiang Z, Tian J, Wang T and Song S. Bone metabolism markers: indicators of loading dose intravenous ibandronate treatment for bone metastases from breast cancer. Clin Exp Pharmacol Physiol 2017; 44: 88-93.
[20] Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, Ripamonti CI and Committee EG. Management of cancer pain in adult patients: ESMO clinical practice guidelines. Ann Oncol 2018; 29: iv166-iv191.
[21] Webster LR and Fine PG. Review and critique of opioid rotation practices and associated risks of toxicity. Pain Med 2012; 13: 562-570.
[22] Vassiliou V, Kalogeropoulou C, Christopoulos C, Solomou E, Leotsinides M and Kardamakis D. Combination ibandronate and radiotherapy for the treatment of bone metastases: clinical evaluation and radiologic assessment. Int J Radiat Oncol Biol Phys 2007; 67: 264-272.
[23] Cleeland CS. The impact of pain on the patient with cancer. Cancer 1984; 54: 2635-2641.
[24] Mantyh PW. Bone cancer pain: from mechanism to therapy. Curr Opin Support Palliat Care 2014; 8: 83-90.
[25] Epplen R, Stockle M, Engelmann U, Heidenreich A and Ohlmann CH. Differential effects of ibandronate, docetaxel and farnesol treatment alone and in combination on the growth of prostate cancer cell lines. Acta Oncol 2011; 50: 127-133.
[26] Karlic H, Thaler R, Gerner C, Grunt T, Proestling K, Haider F and Varga F. Inhibition of the mevalonate pathway affects epigenetic regulation in cancer cells. Cancer Genet 2015; 208: 241-252.
[27] Bianchi M, Franchi S, Ferrario P, Sotgiu ML and Sacerdote P. Effects of the bisphosphonate ibandronate on hyperalgesia, substance P, and cytokine levels in a rat model of persistent inflammatory pain. Eur J Pain 2008; 12: 284-292.
[28] Body JJ, Diel IJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA, Budde M and Bergstrom B; MF 4265 Study Group. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast

cancer and bone metastases. Ann Oncol 2003; 14: 1399-1405.
[29] Diel IJ, Body JJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA, Budde M and Bergstrom B; MF 4265 Study Group. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer 2004; 40: 1704-1712.
[30] Dumon JC, Journe F, Kheddoumi N, Lagneaux L and Body JJ. Cytostatic and apoptotic effects of bisphosphonates on prostate cancer cells. Eur Urol 2004; 45: 521-528; discussion 528-529.
[31] Fisher JE, Rosenberg E, Santora AC and Reszka AA. In vitro and in vivo responses to high and low doses of nitrogen-containing bisphosphonates suggest engagement of different mechanisms for inhibition of osteoclastic bone resorption. Calcif Tissue Int 2013; 92: 531-538.
[32] von Moos R, Caspar CB, Steiner R, Angst R, Inauen R, Schmieding K and Thurlimann B. Long-term renal safety profile of ibandronate 6 mg infused over 15 minutes. Onkologie 2010; 33: 447-450.
[33] Pivot X, Lortholary A, Abadie-Lacourtoisie S, Mefti-Lacheraf F, Pujade-Lauraine E, Lefeuvre C, Letessier S, Morvan P, Dur C and Frimat L. Renal safety of ibandronate 6 mg infused over 15 min versus 60 min in breast cancer patients with bone metastases: a randomized open-label equivalence trial. Breast 2011; 20: 510-514.
[34] Bergner R, Henrich DM, Hoffmann M, Honecker A, Mikus G, Nauth B, Nagel D and Uppenkamp M. Renal safety and pharmacokinetics of ibandronate in multiple myeloma patients with or without impaired renal function. J Clin Pharmacol 2007; 47: 942-950.