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BISPHOSPHONATES IN THE THERAPY OF BONE METASTASES FROM SOLID TUMORS

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Summary

Bisphosphonates (BPs) are drugs that prevent bone loss in the bones affected by malignant disease. Bone homeostasis is maintained by the activity of osteoblasts and osteoclasts. It is generally accepted that activation of osteoclasts is a key step in the emergence and development of bone metastases, and that bone resorption is important not only in classical lithic lesions but also in osteoblastic bone metastases. BPs inhibit osteoclast activity and stimulate osteoclast apoptosis. Thus, osteoclasts are a key therapeutic target in the treatment of bone metastases. Therefore, the use of BPs is a standard form of treatment and prevention of complications associated with bone metastases in patients with malignant tumors, regardless of the primary.

The greatest experience in the treatment of bone metastases from breast cancer is by intravenous BPs such as zolendronic acid, pamidronate and ibandronat. All of them show clinical activity. Until recently, randomized, placebo-controlled studies with BPs did not show a significant reduction in skeletal complications of bone metastases of prostate cancer. However, in the treatment of advanced hormone-resistant prostate cancer, zolendronic acid showed a reduction in the overall risk of skeletal complications by 36% and reduced the intensity of pain. The use of BPs in the treatment of bone metastases of other solid tumors has not been confirmed by randomized placebo-controlled studies. One study has shown a reduction in the incidence of bone metastases and their complications by about 30%. Patients with other tumors and symptomatic bone metastases may also be candidates for treatment with zolendronic acid, especially if bone metastases are a dominant site of metastasis and, if the expected survival is longer than 6 months. Patients with bone metastases of kidney cancer have a special benefit from BP therapy. Despite the apparent clinical benefit from the use of BPs, it is clear that they only play a part in preventing bone metastases and their complications, and some patients in spite of bone metastases never develop complications. Nowadays, one cannot predict which patients will benefit from BPs. Criteria are needed to define when BPs should be started and when they should be stopped. Before the administration of BPs, a primary disease, the extent of bone disease, expected survival, the probability that a patient would experience complications related to bone metastases should be taken into consideration.

KEYWORDS: *bone metastases, bisphosphonates*

BISFOSFONATI U LIJEČENJU KOŠTANIH METASTAZA

Sažetak

Bisfosfonati (BPs) su lijekovi koji sprječavaju gubitak koštane mase u kostima zahvaćenim zloćudnom bolešću. Koštanu homeostazu održava aktivnost osteoblasta i osteoklasta. Opće je prihvaćeno da je aktivacija osteoklasta ključni korak za pojavu i razvoj koštanih metastaza te da je resorpcija kosti važna ne samo kod klasičnih litičnih lezija nego i kod osteoblastičnih koštanih metastaza. Bisfosfonati priječe aktivnost i potiču apoptozu osteoklasta. Dakle, osteoklasti su glavna terapijska meta u liječenju koštanih metastaza. Primjena bisfosfonata standardni je oblik liječenja i prevencije komplikacija povezanih s koštanim metastazama u bolesnika sa zloćudnim tumorima bez obzira na primarno sijelo.

Najviše iskustva u liječenju koštanih metastaza raka dojke stečeno je pri intravenskoj primjeni bisfosfonata i to zolendronične kiseline, pamidronata i ibandronata. Svi oni pokazuju kliničku aktivnost. Randomizirana, placebom kontrolirana klinička ispitivanja bisfosfonata donedavno nisu upućivala na značajnije smanjenje komplikacija prouzročenih

koštanim metastazama raka prostate. Međutim, u liječenju uznapredovanog raka prostate otpornog na hormone pokazalo se da zolendronična kiselina smanjuje i ukupan rizik komplikacija u kostima za 36% i jačinu boli. Korist primjene bisfosfonata u liječenju koštanih metastaza drugih solidnih tumora nije potvrđena u randomiziranim, placebom kontroliranim ispitivanjima. U jednom je ispitivanju uočeno smanjenje pojavnosti koštanih metastaza i komplikacija za otprilike 30%. U bolesnika s drugim tumorima i simptomatičnim koštanim metastazama također bi se moglo primijeniti liječenje zolendroničnom kiselinom, osobito ako su koštane metastaze dominantno sijelo metastaza te ako je očekivano preživljenje dulje od 6 mjeseci. Bolesnicima s koštanim metastazama raka bubrega terapija bisfosfonatima je od posebne koristi. Unatoč očitoj kliničkoj koristi od primjene bisfosfonata, jasno je da oni samo sudjeluju u sprečavanju pojave koštanih metastaza i komplikacija izazvanih koštanim metastazama, a u nekih bolesnika komplikacije nikad me nastupe bez obzira na prisutnost koštanih metastaza. U ovom trenutku nije moguće predvidjeti koji će bolesnici imati koristi od bisfosfonata. Potrebno je utvrditi kriterije prema kojima bi se odredilo kad treba započeti i kad prekinuti primjenu bisfosfonata. Prije primjene bisfosfonata valja uzeti u obzir primarnu bolest, raširenost bolesti u kostima, očekivano preživljenje i vjerojatnost da bi bolesnik mogao imati komplikacije u vezi s koštanim metastazama.

KLJUČNE RIJEČI: *koštane metastaze, bisfosfonati*

INTRODUCTION

Bone metastases are frequent sequelae of common solid tumors because the bone microenvironment provides a fertile soil for the growth of human cancer cells (1). The clinical complications of bone metastasis can lead to severe bone pain, impaired mobility, pathologic fractures, and spinal cord compression. Moreover, once tumor cells have become embedded in the skeleton, cure is no longer possible, and only palliative therapy is available (1).

The overall extent of the problem is that there are approximately 10 million patients around the world with cancer that involves bone (2). Boney involvement is common in patients with breast or prostate cancers where more than two thirds will develop involvement in the bone, as will approximately one third of lung or bladder cancer patients (3). Importantly, bone is often the only site of metastatic disease in cancers that have spread outside the local tumor area, and this is particularly true in breast and prostate cancer (3-5). Equally important is the fact that patients plagued with bone metastases often live not for weeks or months but for many years with the morbidities of boney involvement and the side effects that can occur with treatment. This is of major clinical consequence because of the chronicity of the problem for the patients themselves, caregivers or families, and society in general because of the cost (3-5). Median of survival of patients with bone metastases is 6 months for patients with lung or bladder cancer, 12 months for patients with kidney cancer, 19-25 months for patients with breast cancer and almost 4 years for patients with prostate cancer (3-5).

HEALTHY BONE

Bones are composed of three components: 65% are minerals (cortex bone is composed of calcium, magnesium, phosphate, carbonate, hydroxyl fluoride and citrate), 35% is organic part (bone matrix consists mainly of connective tissue; collagen is insoluble fibrous protein, which accounts for 90% of the matrix and uncalcified matrix is called osteoid) and cells (osteoclasts, osteoblasts, osteocytes, osteoclasts at rest or so-called "lining cells" (6). Bone is a living organ with persistent remodeling. It is a process that takes 3-5 months and is divided into 3 parts: bone resorption by osteoclasts, bone formation by osteoblasts and bone mineralization (7). In a different age, different process of remodeling prevails. For example, in childhood formation of bone is dominant and bone grows, in adult bone formation is in equilibrium with bone resorption which maintains bone health, in older age or illness the bone resorption predominates and reduces bone strength (7).

PATHOGENESIS OF BONE METASTASES

There are 3 varieties of metastatic bone lesions in solid tumors: osteolytic, osteoblastic, or mixed. For example, in breast cancer most patients have osteolytic metastatic disease, but in approximately 15% to 20% of cases patients will have predominantly osteoblastic lesions. In certain other cancers, for example of the kidney or thyroid, the lesions may be primarily lytic. In prostate cancer, on the other hand, most patients have osteoblastic lesions. It is important to note that the same pa-

tient may have all types of lesions (8). The most common sites of metastatic bone lesions are thoracolumbar spine, pelvis and proximal femur (9).

What is the pathogenesis of osteolytic bone metastases? Malignant cells that have colonized the favorable microenvironment of bone can secrete a multitude of soluble factors that affect bone formation and distort normal, balanced bone remodeling. The various peptides, growth factors, cytokines, and proteins released by tumor cells, including parathyroid hormone-related protein (PTHrP), prostaglandin E, and procathepsin D, can stimulate osteoclasts directly or indirectly to degrade bone. The activated osteoclasts in turn release other soluble growth factors, such as transforming growth factor beta (TGF-β) and interleukin-6 (IL-6), which stimulate tumor-cell growth.

The reciprocal actions of PTHrP and TGF-β perpetuate a vicious cycle of bone destruction, with the patient experiencing bone loss and weakened bone structure (10).

What is the pathogenesis of osteoblastic bone metastases? Tumor cancer cells produce a variety of factors, including proteases and cytokines that have potent impacts on bone. In particular, these growth factors promote the growth of osteoblasts. This so-called vicious cycle results in dysfunctional new bone formation; notably, the new bone formed in osteoblastic metastases is disorganized and biomechanically weak. Despite the fact that the lesions may be more dense or sclerotic, the bones are fragile and at risk for complications such as fractures (11).

CLINICAL ASPECTS OF BONE METASTASES

The clinical consequences of cancer-induced bone disease are fractures of the nonvertebral bones or vertebral compression fractures, spinal cord compression or collapse, the need for radiation therapy to treat bone disease, the need for surgery to treat bone disease or prevent fractures, and hypercalcemia. All of these are considered skeletal-related events (SREs). Bone pain may result from boney involvement, and often patients require pain medications. This may impact quality of life and also directly impact overall survival (12).

Without treatment SREs occur on average every eight months. The median time to first SRE is eleven months and over 24 months, nearly 50% patients with bone metastases experience SREs (13). As the patients live longer, it is more likely that SREs occur. SREs cause a decrease in QOL and reduce survival of patients with cancer (13). It is important to note that patients with metastatic bone disease survive many years and patients are concerned that bone metastasis can lead to SREs. In the setting of breast cancer, during a 1-year period, 50% of patients with bone metastases and without therapy, experienced a major complication such as fracture, severe pain requiring radiotherapy, cord compression, hypercalcemia of malignancy, or the need for orthopedic surgery. Reducing these common events benefits patient and reduces healthcare costs (11). The negative impact of boney complications on patients include increased medical costs associated with treatment and impaired mobility. Hip fracture alone results in a 50% disability rate, and 25% of patients will require nursing home care. In addition, the history of a skeletal complication is associated with a lower quality of life (14).

MANAGEMENT OF METASTATIC BONE DISEASE

The management of metastatic bone disease requires a multidisciplinary approach. The oncologist, surgeon, orthopedist, neurosurgeon, nuclear medicine specialist, pain specialist, rehabilitation/physical medicine doctor, or physical therapist may all be part of the team to help the cancer patient with bone disease (15). Radiotherapy is used to treat bone pain to relieve neurologic complications from, for example, spinal cord compression (16). Bone-seeking radioisotopes have been approved to reduce bone pain (17). Surgery is used to treat a pathological fracture, to prevent an impending fracture, or to reduce neurologic complications from spinal cord compression. Less invasive surgical procedures, including vertebroplasty and kyphoplasty, help to stabilize the vertebral compression body involved in vertebral compression fractures, and result in less bone pain (18). Analgesia, used to reduce bone pain, is highly effective, but it may have significant treatment-associated morbidity (19). Bisphosphonates (BPs) have been the mainstay of treatment, and i.v. BP has been shown not only to reduce bone pain but to reduce the occurrence of new SREs (20).

BP THERAPY FOR METASTATIC BONE DISEASE

Through a variety of direct and indirect inhibitory actions on osteoclasts, such as maturation and recruitment to bone surface, BPs prevent and delay the onset of skeletal complications and reduce their incidence. Similarly, through their effects on osteoblasts, tumor cells, and cytokine and growth-factor production, they may interrupt the vicious cycle of bone destruction and restore balance to osteoclast and osteoblast activity. This inhibition of pathologic bone resorption significantly reduces pain and the need for radiation and/or bone surgery (20-22).

In general, BPs are potent inhibitors of bone loss. Their potency varies greatly depending on their R1 and R2 side chain groups. BPs lacking a nitrogen in their side chains (i.e. clodronate) are relatively impotent drugs, but introduction of a nitrogen in the R2 side chain (i.e. pamidronate, ibandronate, zolendronic acid) increased their ability to reduce skeletal complications. Importantly, oral administration of BPs is fraught with reduced absorption, whereas intravenously these drugs have marked potency (23).

The effects of different BPs on bone resorption were measured in animal studies. The BP dose required to reduce hypercalcemia by 50% was evaluated in the hypercalcemic rat model. Zolendronic acid was the most potent BP tested *in vivo*, with up to 850 times greater activity than conventional BPs. These data correlated with those in mouse calvaria studies *in vitro.* The correlation between the *in vitro* and *in vivo* assays confirms that the pharmacodynamic action of zolendronic acid is due to direct inhibition of bone resorption *in vivo* (24).

SIDE-EFFECTS OF BPS

An important concept with BPs is anti–bone resorptive potency vs renal dysfunction. It is important to recognize that bisphosphonate-associated renal dysfunction, although infrequent, can occur with any of the BPs and relates to the backbone, not the R2 side chain responsible for anti–bone resorptive potency. Therefore, more potent drugs are not more kidney toxic. It is important to note with respect to renal function that the safe use of BPs is related to the rate of infusion (25). Changes in kidney function are related to Cmax, the maximum concentration of the BP achieved in the blood, which is related to the rate the drug is given. An administration rate faster than approximately one half milligram per minute can lead to kidney problems, but the rate of infusion has no impact on ability to prevent skeletal complications. The area under the concentration curve – that is, the amount of drug remaining in the patient – gives it its efficacy. Simply stated, zoledronic acid administered over a minute, an hour, or a day is equally effective but has a different risk on the kidney toxicity. The same holds true with pamidronate. Zoledronic acid and pamidronate affect different parts of the kidney. Zoledronic acid largely affects the tubular function and pamidronate largely affects the glomerular function. To reduce the risk of renal dysfunction, serum creatinine should be monitored prior to each infusion and the patient should be properly hydrated, if necessary, with i.v. fluids before BP treatment is initiated (26). Adverse effects on the kidney occur at similar rates of infusion for zoledronic acid or pamidronate. However, the effective dose of zoledronic acid in the setting of metastatic bone disease is 4 mg, which can be given over 15 minutes, compared with the 90-mg dose required for pamidronate, which takes about 2 hours to administer safely. It is recommended to change the dose of zoledronic acid and perhaps pamidronate based on the creatinine clearance, but this does not make a lot of sense since it is the infusion time and not the actual dose that is the determinant factor for renal risk. Patients should get 4 mg of zoledronic acid or 90 milligrams of pamidronate, and if there is a concern about renal toxicity risk, the infusion rate should be simply slowed (26). If the serum creatinine is less than 3 mg/dL, there is really no reason to significantly change the dose, infusion time, or schedule. Among patients with worse renal function, pamidronate can be given quite safely. There are ongoing studies for zoledronic acid, but so far it appears to be safe to administer. If the patient is already irreversibly on dialysis and is not going to retrieve renal function, either drug can be used at the same dose, infusion time, and interval as for a patient with normal renal function. These drugs have a very short half-life in the serum, so as long as the patient is not moving from the infusion chair to get dialysis, there will be benefit. If the renal function of a patient with initially

poor renal function reverses with their anticancer therapy, BP can be started. If the patient has hypercalcemia, zoledronic acid should be used regardless of the creatinine reading. It is the drug of choice in this setting as it has been shown to work better than pamidronate in randomized trials (26).

Osteonecrosis of the jaw (ONJ) is exposed dead bone in the maxillofacial area that has not healed after 6 weeks of appropriate evaluation and dental care. It is important to rule out metastatic bone disease of the jaw and radiation to that site as a possible cause for the necrosis of the jawbone (27). The frequency of osteonecrosis of the jaw ONJ in patients with malignant bone disease varies a lot between studies. The frequency is approximately 5.0% or approximately 0.5% to 1.0% risk per year (28-30). Risk factors for ONJ are trauma and dental extractions, but root canals, cavity repair, poor dental hygiene, and i.v. BPs are not. There are some newer data suggesting that antiangiogenic therapies may be an additional risk factor; drugs such as bevacizumab are associated with this complication. To minimize the risk of ONJ, the mouth must be kept healthy. Regular dental exams are important. Alcohol use should be limited and there should be no tobacco use. Ensure the patient has a proper dental exam, and that any necessary dental extractions or implants are done before they start either i.v. pamidronate or zolendronic acid. These procedures should be avoided once i.v. BPs are started (31). Managing ONJ first involves making an accurate diagnosis. The patient may have another complication, such as osteoradial necrosis of the jaw or metastases in the jaw. The severity of the ONJ should be assessed, as this can range from a small piece of exposed bone that is asymptomatic to stage III that is heavily involved with infection and fractures (32). It is important to maintain excellent dental hygiene in patients with ONJ. Surgery should be kept to a minimum, and if surgery is necessary, it should done by properly trained surgeons familiar with ONJ. There is no standard treatment today, although if ONJ becomes secondarily infected, immediate treatment with antibacterials and possibly antifungals and antivirals is certainly indicated and will help overcome the problem. Although hyperbaric oxygen has not formally proven useful, there are some anecdotal cases in favor of it. There is no evidence that stopping i.v. BP is necessary or changes the course of ONJ (33).

OTHER TREATMENT RECOMMENDATIONS FOR PATIENTS WITH BONE METASTASES

Other therapy of bone metastases include reducing the risk of falls in the home by making sure that the patients are in a setting in which they do not have loose rugs or slippery floors, encouraging weight-bearing exercise which will improve bone density, physical therapy with weight-bearing techniques, and, of course, oral vitamin D and calcium. This last point is important and it should be emphasized that many patients with myeloma and other cancers metastatic to bone have low vitamin D levels. Vitamin D levels should be checked and, if low, should be replaced with much higher amounts than the 800 units daily indicated here (34).

ACTIVITY OF BP IN DIFFERENT BONE METASTASES FROM SOLID TUMORS

All of the BPs have shown activity in advanced breast cancer. Meta-analysis which included 21 studies in metastatic breast cancer has shown that zolendronic acid, pamidronate, and clodronate were all able to significantly reduce the risk of SREs compared with placebo or no BP therapy in patients with bone metastases of breast cancer (35). Ibandronate also significantly reduced the incidence of SREs but to a lesser degree (36,37). The older clodronate trials were not statistically significant individually but showed clinical benefit when the data were pooled (38-40). The analysis also included 2 European trials of biannual intravenous ibandronate or 15 mg of daily oral ibandronate, and the placebo-controlled pamidronate trials published by Hortobagyi and Theriault in the 1990s, which demonstrated a highly significant reduction in SRE rates (36, 37, 41, 42). The only placebo-controlled zolendronic acid trial was conducted in Japan and showed a 41% reduction in the risk of a SRE, a result that appears to outperform all other agents used to date (43).

Clodronate i.v. appeared to relieve bone pain in 16 of 17 patients with bone metastases of prostate cancer in an uncontrolled study, and oral clodronate added to estramustine phosphate improved pain relief in correlation with decreases in levels of markers of bone destruction in the same patient population (44-46). Pamidronate demon-

strated clinical reductions in bone pain that could be predicted by changes in markers of bone destruction in 10 patients and significant reductions in self-reported pain in patients with decreasing/stable analgesic use but not in those with increasing analgesic use (47). Lipton et al. reported a study of 58 patients with prostate cancer treated with increasing doses of pamidronate. They noted no dose-response relationship, no change in bone markers, and no healing of lesions (48).

In a small open-label, non-randomized study, i.v. ibandronate was shown to be effective for reducing pain from prostate cancer metastasized to bone. Efficacy in terms of reduction of SREs was not measured (49).

Study 039 with zolendronic acid in metastatic bone disease of prostate cancer has shown a significant reduction of SRE (p=0.021), significant improvement of time to first SRE (p=0.011), significant decrease in pain score (p=0.003) and significant decrease in bone resorption markers level (p=0.001) (48). Based on these data and available evidence demonstrating a significantly lower incidence of skeletal complications as well as durable pain palliation, zolendronic acid is presently the BP treatment of choice for patients with hormone refractory prostate cancer metastatic to bone (48).

Osteoclast activity in prostate cancer predicts bad outcome of the disease (50). In phase III study with zolendronic acid in therapy of bone metastases of prostate cancer, in the zolendronic acid group, the median percent change in the N-telopeptide/creatinine ratio and deoxypyridinoline/creatinine ratio showed a consistent marked decrease from baseline compared with increases in the placebo group. In the zolendronic acid treatment arm, the serum bone alkaline phosphatase levels, which are frequently elevated in patients with prostatic cancer, were consistently decreased from baseline, whereas those in the placebo group continued to increase throughout the study. These differences were statistically significant at all timepoints for the between-treatment comparisons, implying persistence of efficacy of zolendronic acid in preventing malignant bone resorption and bone formation. However, current evidence does not support the use of bone markers as basis for clinical decision making (48, 50).

Renal cell cancer with lymph node metastases at primary diagnosis often metastasizes to bone. Bone morbidity among patients with kidney cancer during the first year is similar to that in patients with breast cancer or multiple myeloma (2.5 up to 4.0 SREs per patient per year) (5). A phase II study with zolendronic acid in patients with bone metastases of kidney cancer has shown 58% decrease of development of SREs (5). Zolendronic acid reduced risk of developing a SRE by 31% in a double-blind, placebo controlled, 21-month trial that included 773 patients with lung cancer and other solid tumors (51).

CONCLUSION

Bone metastases result from complex interactions between cancer cells, bone cells, and stem cells in the bone marrow microenvironment. BPs are an important component of metastatic bone disease management; they reduce the number and severity of skeletal complications and can be used effectively to prevent cancer treatment-induced bone loss. Promising data suggest that BPs may also prevent or interrupt the metastatic process and reduce recurrence rates.

REFERENCES

1. Mundy GR. Mechanisms of bone metastasis. Cancer 1997;80:1546-56.
2. Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94 (2):153-6.
3. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001; 27:165-76.
4. Coleman RE. Skeletal complications of malignancy. Cancer 1997;80:1588-94.
5. Zekri J, Ahmed N, Coleman RE, et al. The skeletal metastatic complications of renal cell carcinoma. Int J Oncol 2001; 19: 379-82.
6. Kalkwarf HJ, Zemel BS, Gilsanz V, et al. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. J Clin Endocrinol Metab 2007;92(6):2087-99.
7. Henriksen K, Neutzsky-Wulff AV, Bonewald LF, et al. Local communication on and within bone controls bone remodeling. Bone 2009;44(6):1026-33.
8. Roodman GD. Mechanisms of bone metastasis. N Engl J Med 2004;350:1655-64.
9. Berenson JR, Rajdev L, Broder M. Pathophysiology of bone metastases. Cancer Biol Ther. 2006;5(9):1078-81.
10. Orr FW, Lee J, Duivenvoorden WC, et al. Pathophysiologic interactions in skeletal metastasis. Cancer 2000; 88:2912-8.

11. Goltzman D. Mechanisms of the development of osteoblastic metastases. Cancer 1997;80:1581-7.
12. Weinfurt KP, Castel LD, Li Y, et al. Health-related quality of life among patients with breat cancer receiving zolendronic acid or pamidronate disodium for metastatic bone lesions. Med Care 2004;42:164-75.
13. Oefelein MG, Ricchiuti V, Conrad W, et al. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. J Urol 2002;168:1005-7.
14. Saad F, Olsson C, Schulmann CC. Skeletal morbidity in men with prostate canecr: quality of life consideration throughout the continuum of care. Eur Urol 2004;46:731-40.
15. Ibrahim T, Flamini E, Fabbri L, et al. Multidisciplinary approach to the treatment of bone metastases: Osteo-Oncology Center, a new organizational model. Tumori 2009;95:291-7.
16. Kijima T, Fujii Y, Suyama T, et al. Radiotherapy to bone metastases from renal cell carcinoma with or without zoledronate. BJU Int 2009;103:620-4.
17. Silberstein EB. Teletherapy and radiopharmaceutical therapy of painful bone metastases. Semin Nucl Med 2005;35:152-8.
18. Dürr HR, Müller PE, Lenz T, et al. Surgical treatment of bone metastases in patients with breast cancer. Clin Orthop Relat Res 2002;396:191-6.
19. Brogan S, Junkins S. Interventional therapies for the management of cancer pain. J Support Oncol 2010;8: 52-9.
20. Berenson JR, Lipton A. Bisphosphonates in the treatment of malignant bone disease. Annu Rev Med 1999; 50:237-48.
21. Boissier S, Ferreras M, Peyruchaud O, et al. Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases. Cancer Res 2000;60:2949-54.
22. Adami S. Bisphosphonates in prostate carcinoma. Cancer 1997;80:1674-9.
23. Russell RG, Watts NB, Ebetino FH, et al. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 2008;19:733-59.
24. Green JR, Müller K, Jaeggi KA. Preclinical pharmacology of CGP 42'446, a new, potent, heterocyclic bisphosphonate compound. J Bone Miner Res 1994;9:745-51.
25. Oh WK, Proctor K, Nakabayashi M, et al. The risk of renal impairment in hormone-refractory prostate cancer patients with bone metastases treated with zoledronic acid. Cancer 2007;109:1090-6.
26. Berenson JR, Rosen L, Vescio R, et al. Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. J Clin Pharmacol 1997;37:285-90.
27. Weitzman R, Sauter N, Eriksen EF, et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients--May 2006. Crit Rev Oncol Hematol 2007;62:148-52.
28. Khan AA, Sándor GK, Dore E, et al. Bisphosphonate associated osteonecrosis of the jaw. J Rheumatol 2009; 36:478-90.
29. Zervas K, Verrou E, Teleioudis Z, et al. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. Br J Haematol 2006;134:620-3.
30. Dimopoulos MA, Kastritis E, Anagnostopoulos A, et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. Hematologica 2006;91:968-71.
31. Gross HB. Bisphosphonate-induced osteonecrosis: dental considerations. Compend Contin Educ Dent 2008;29:112-3.
32. Ruggiero SL, Mehrotra B. Bisphosphonate-related osteonecrosis of the jaw: diagnosis, prevention, and management. Annu Rev Med 2009;60:85-96.
33. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006; 102:433-41.
34. Janjan N. Bone metastases: approaches to management. Semin Oncol 2001;28:28-34.
35. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. Cochrane Database Syst Rev 2005;3: CDC003474.
36. Body JJ, Diel IJ, Lichinitzer M, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer 2004;90:1133-7.
37. Tripathy A D, Diel I, Body JJ. Ibandronate reduces skeletal morbidity in patients with breast cancer. Semin Oncol 2004;31:64-6.
38. Kristensen B, Ejlertsen B, Groenvold M, et al. Oral clodronate in breast cancer patients with bone metastases: a randomized study. J Intern Med 1999;246:67-7.
39. Paterson AH, Powles TJ, Kanis JA, et al. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. J Clin Oncol 1993;11: 59-65.
40. Tubiana-Hulin M, Beuzeboc P, Mauriac L, et al. Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases. Bull Cancer 2001;88:701-7.
41. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group J Clin Oncol 1998;16: 2038-44.
42. Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a ran-

domized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol 1999;17: 846-54.
43. Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. J Clin Oncol 2005;23:3314-21.
44. Adami S, Salvagno G, Guarrera G, et al. Dichloromethylene-diphosphonate in patients with prostatic carcinoma metastatic to the skeleton. J Urol 1985;134: 1152-4.
45. Heidenreich A, Hofmann R, Engelmann UH. The use of bisphosphonate for the palliative treatment of painful bone metastasis due to hormone refractory prostate cancer. J Urol 2001;165:136-40.
46. Rodrigues P, Hering F, Campagnari JC. Use of bisphosphonates can dramatically improve pain in advanced hormone-refractory prostate cancer patients. Prostate Cancer Prostatic Dis 2004;7:350-4.
47. Vinholes JJ, Purohit OP, Abbey ME, et al. Relationships between biochemical and symptomatic response in a double-blind randomized trial of pamidronate for metastatic bone disease. Ann Oncol 1997;8:1243-50.
48. Lipton A, Small E, Saad F, et al. The new bisphosphonate, ZOMETA (zoledronic acid), decreases skeletal complications in both lytic and blastic lesions: a comparison to pamidronate. Cancer Invest 2002;20:45-54.
49. Heidenreich A, Elert A, Hofmann R. Ibandronate in metastatcis bone pain. Semin Oncol 2004;31:67-72.
50. Lipton A, Cook R, Saad F, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. Cancer 20081;113:193-201.
51. Rosen LS, Gordon D, Tchekmedyian S, et al. Zolendronic acid versus placebo in treatment of skeletal metastases in patients with lung cancer and other solid tumours: a phase III, double-blind, randomized trial-the Zolendronic Acid Lung Cancer and Other Solid Tumors Study Group. J Clin Oncol 2003;21:3150-7.

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