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The science behind metastatic bone pain

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ABSTRACT

Metastatic bone pain is a significant cause of morbidity in patients with advanced cancer and greatly reduces quality of life. Standard palliative treatments such as opioids may not provide effective relief of metastatic bone pain, particularly acute breakthrough pain, without unacceptable side effects at the high doses required. A mouse model of metastatic bone pain has been developed in which tumor cells are injected directly into the marrow space of mice femora. As the tumor cells proliferate, mice display reproducible behaviors associated with pain, such as flinching or guarding the affected limb, that increase as bone destruction progresses. The model also enables measurement of other endpoints, including tumor growth and migration, and monitoring of relevant cell types such as osteoclasts, macrophages, and neurons. Mouse studies have provided important information on the mechanisms behind metastatic bone pain and the specific effects of potential therapies. These studies have demonstrated that metastatic bone disease is caused by multiple factors and that osteoclasts are particularly important in pain generation through destruction of bone and nerve fibers and acidotic stimulation of pH-sensitive receptors. Clinical studies with bisphosphonates demonstrate that these agents provide relief of metastatic bone pain, and preliminary experiments using the mouse model suggest that this may occur via multiple mechanisms. Further studies are under way.

1. Introduction

Pain is a highly debilitating symptom for patients with cancer, causing disability, immobility, and reduced quality of life. Bone metastases are the most common cause of cancer pain,[1] and up to two-thirds of patients with bone metastases will suffer severe pain.[2] Effective treatments for metastatic bone pain (MBP) are therefore an essential part of cancer care.

MBP is a progressive condition. Most patients initially experience intermittent dull aches, and over a period of weeks or months, this becomes progressively more severe and constant.[1,3] In addition, most patients with bone metastases experience acute episodes of severe breakthrough pain that are often localized to a particular area.[4,5] The most common cause of breakthrough pain is movement during normal activities such as turning in bed, standing, sitting, or coughing; however, breakthrough pain can also be unrelated to activity and less predictable. The degree of pain experienced by patients cannot be predicted by tumor type, size, or location or by number of bone metastases, and the pain produced by a bone lesion is often disproportionate to the degree of bone involvement.[1] It is therefore likely that MBP has a complex etiology. As cancer pain progresses in severity, it becomes increasingly detrimental to a patient's quality of life.

Recommendations from the World Health Organization state that patients should receive treatment for cancer pain according to a three-step analgesic ladder with the aim of achieving freedom from pain.[6,7] The ladder comprises non-opioid analgesics (e.g., aspirin and acetaminophen) for mild cancer pain, weak opioids (e.g., codeine) for moderate pain,

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and strong opioids (e.g., morphine) for severe pain, in addition to adjuvant treatments. However, freedom from severe breakthrough pain caused by bone metastases is rarely achieved because patients titrate their opioid doses to avoid the significant side effects of high doses, such as constipation or sedation.[8,9] Although radiotherapy may assist in providing pain relief for patients with localized MBP, there is still a significant need for improved pain-relief strategies.

2. Development of metastatic bone cancer

Bone is a common metastatic site.[10,11] Metastatic cells from the primary tumor, e.g., breast or prostate cancers, have a high likelihood of being carried to bone because of the high blood flow in bone tissue. Tumor cells express adhesive molecules on their surfaces that enable binding to marrow stromal cells and bone matrix. In addition, bone is a rich source of immobilized growth factors that promote tumor cell proliferation once metastatic cells have become resident. As bone metastases grow, they release various factors that stimulate the activity of osteoclasts or osteoblasts, leading to bone destruction or formation, respectively, and disruption of the normal bone remodeling process. It is this disruption that is the main cause of metastatic bone disease and its resulting sequelae, such as fractures and hypercalcemia. Metastasis to bone frequently occurs before a patient is aware that they have cancer, and MBP is often the first symptom to alert a patient to the disease.

Traditionally, bone metastases have been classified as either osteolytic (bone destroying) or osteoblastic (bone forming). It is now clear that these activities are linked and that almost all metastatic tumors induce a combination of bone destruction and formation, with the overall phenotype indicative of the predominating activity induced by the individual tumor (Fig. 1).[10,11] Although prostate cancer causes mainly osteoblastic lesions, analysis of bone markers has demonstrated that this tumor has some of the highest levels of bone destruction of any tumor type.[12]

3. Mouse model of metastatic bone pain

To investigate the mechanisms behind MBP, a mouse model has been developed.[13–15] Tumor cells are injected directly into the femoral marrow space and retained using dental amalgam, which prevents invasion of adjacent soft tissues (Fig. 2). As the tumor develops, the resulting bone lesions become radiologically apparent (Fig. 3). Injection of different types of tumor cells results in altered patterns of bone lesions, mirroring the clinical picture in patients with different primary cancers. Injected mice display pain-associated behaviors such as flinching or guarding of the affected limb that are reproducible and can be quantified during experimental analysis (Fig. 4). Pain behaviors are spontaneous but can be exacerbated by palpation, similar to movement-induced breakthrough pain in humans, and the extent of pain-associated behavior correlates with the degree of bone destruction.

In addition to pain-associated behaviors and bone destruction, the murine model of MBP has other measurable endpoints. Tumor cells can be stably transfected with a fluorescent marker enabling observation of tumor growth and migration within the bone (Fig. 5), which indicates disease progression. In addition, well-characterized markers are available for many relevant cell types. These have demonstrated that bone lesions are characterized by osteoclast pro-

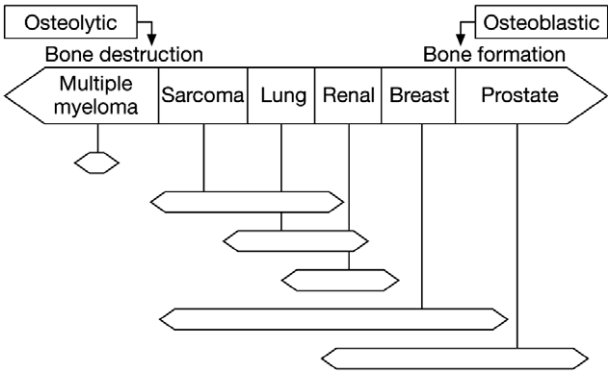

Fig. 1 – Spectrum of bone lesion characteristics in various types of cancer.

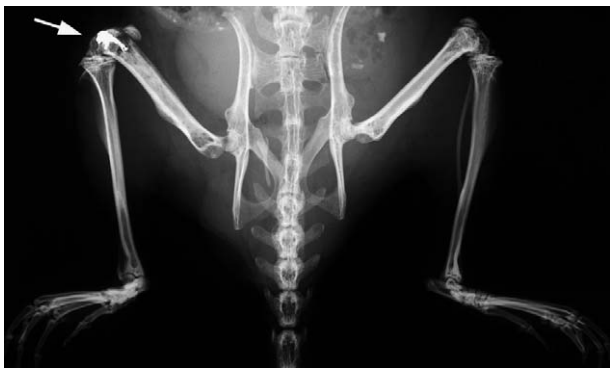

Fig. 2 – Radiograph of mouse pelvis and hind limbs after injection of sarcoma cells into the femur. The amalgam plug retaining the tumor cells within the femur is visible (arrow).[19]

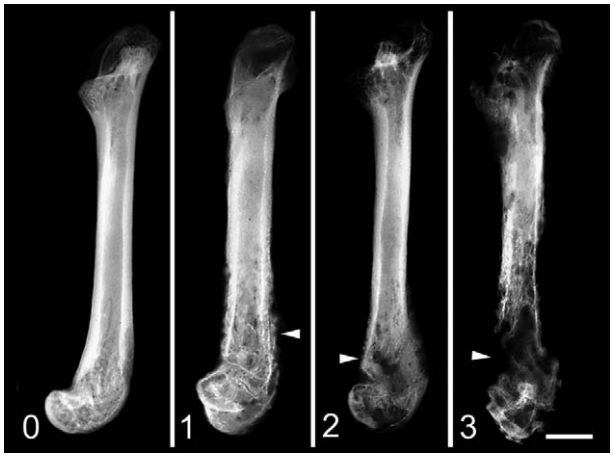

Fig. 3 – Radiographs of murine femora showing the progressive loss of mineralized bone caused by tumor growth. Numbers indicate weeks post injection. Scale bar = 2 mm.[37]

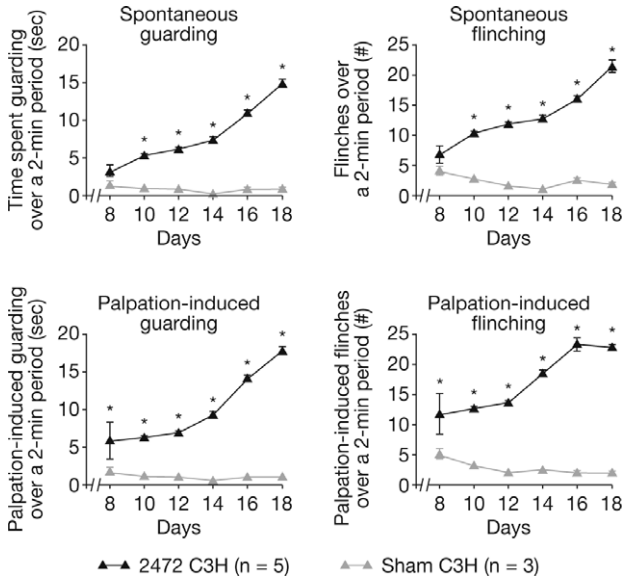

Fig. 4 – Changes in pain behavior over time following tumor cell injection (2472 sarcoma cells) into the femur of C3H mice compared with sham injection (*P < 0.05).

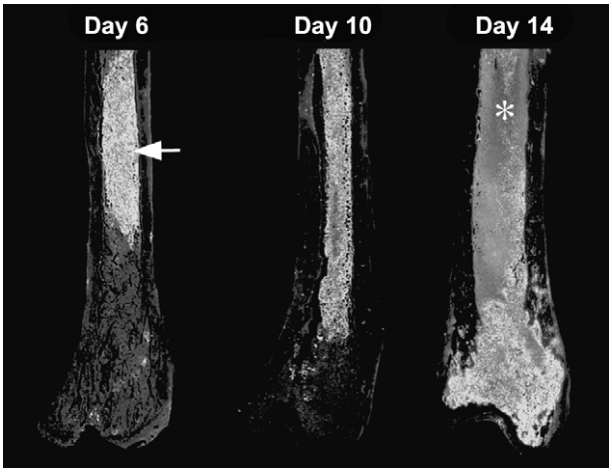

Fig. 5 – Progression of fluorescent-labeled sarcoma cells on different numbers of days post injection into a mouse femur. On day 6, tumor cells remain close to the injection site (indicated by arrow). By day 14, cells have proliferated and migrated throughout the entire marrow space (original injection site indicated by *).

liferation or hypertrophy, macrophage infiltration, and neuronal injury or reorganization.[13–15] Combining measures of behavior, bone destruction, and cellular activity allows a more comprehensive understanding of the pathophysiology of MBP.

An important question is how closely the mouse model mirrors the principal characteristics of MBP in humans. It is clear that the model displays several key features of clinical disease, such as pain behaviors and tumor progression.[13] In addition, similarities have been observed regarding the relative efficacy of treatments. In humans, much higher doses of opioids are required to alleviate MBP than to relieve inflammatory pain. When this was assessed in the mouse model, the morphine dose required to block bone tumor-induced pain behaviors was 10-fold higher than the dose required to block inflammatory pain behaviors of similar magnitude induced by hindpaw injection of Freund's adjuvant.[16] This illustrates that the model has the potential to provide information on the possible clinical efficacy of novel palliative therapies for MBP.

4. The role of osteoclasts in metastatic bone pain

Mouse studies have provided important insights into the mechanisms behind bone cancer pain in humans (Fig. 6). It is clear that the osteoclast, as the cell primarily responsible for bone destruction in metastatic disease, plays a central role in pain generation via several mechanisms.[13–15] Bone tissue, including the periosteum (outer bone covering), mineralized bone, and marrow, is extensively innervated by sensory neurons. Osteoclast-induced bone destruction leads to bone destabilization, which causes pain through stimulation of mechanosensitive receptors in the periosteum. In addition, osteoclasts create an acidic microenvironment during the bone resorption process, stimulating pH-sensitive receptors. Excessive osteoclast activity leads to destruction of sensory fibers, causing neuropathic pain.[17] Because osteoclast activation and proliferation are features of both osteolytic and osteoblastic bone metastases, osteoclasts may play a role in pain generation even when excessive bone loss does not occur. The osteoclast is therefore an attractive target for MBP therapies. Importantly, mouse studies have demonstrated that inhibiting osteoclast activity can reduce or prevent pain-associated behaviors.[18–20]

MBP can be driven by other factors.[3,13–15] Tumor growth can cause pain through bone distention, which can result in mechanical stress and sensory neuron compression. A large proportion of the tumor mass may be composed of inflammatory cells (e.g., macrophages). Both tumor cells and inflammatory cells secrete a variety of cytokines and other factors, including prostaglandins, endothelins, and nerve growth factor. Sensory neurons in bone express receptors that detect

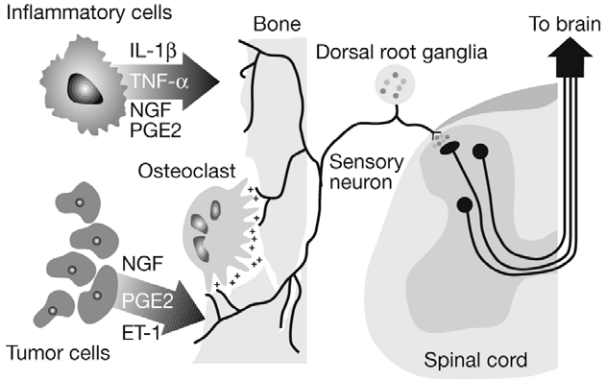

Fig. 6 – Mechanisms driving metastatic bone pain (adapted from Ref. [13]). Abbreviations: ET, endothelin; IL, interleukin; NGF, nerve growth factor; PG, prostaglandin; TNF, tumor necrosis factor.

several of these products, leading to a pain response or pain sensitization. In addition, proton release by inflammatory cells can contribute to local acidosis. The multifactorial nature of bone cancer pain helps explain why the level of pain does not necessarily correspond to the extent of bone involvement and why different therapies are required for pain relief at different stages of disease or for ongoing versus breakthrough pain. Successful therapies need to target the components individually or in combination.

5. Relief of metastatic bone pain with bisphosphonates

Bisphosphonates are a standard treatment for preventing skeletal complications in patients with metastatic bone disease. Because bisphosphonates inhibit osteoclast-induced bone destruction, these agents could potentially be useful for all patients with MBP. Several trials with bisphosphonates have demonstrated a palliative effect.[21–27] In particular, clinical studies have shown that ibandronate, a single-nitrogen, noncyclic bisphosphonate available in intravenous and oral formulations, provides long-term MBP relief for up to 2 years following standard dosing[25–27] and rapid pain relief with intensive dosing on consecutive days (loading dose).[28,29] In all cases, pain relief with ibandronate was associated with significant improvements in patient quality of life.

The mechanisms of action of bisphosphonates in relieving MBP have not been elucidated fully, although they are under active investigation. Alendronate, a bisphosphonate not indicated for metastatic bone disease but widely used for treatment of osteoporosis, is currently the only agent in this class to have been studied in detail in the mouse model.[17] In mice injected with labeled sarcoma cells, alendronate treatment markedly reduced ongoing and movement-evoked pain behaviors, osteoclast activity, tumor-induced bone destruction and resorption, sensory nerve fiber destruction, and neurochemical changes, although overall tumor burden was not affected. Although alendronate is not indicated for metastatic bone disease, these experiments demonstrate that bisphosphonates have multiple effects that may contribute to relief of MBP. Studies using bisphosphonates with clinically proven palliative benefits, such as ibandronate, may reveal more extensive effects. Murine experiments with ibandronate, including loading-dose treatment, are under way. These will also investigate the potential of ibandronate to attenuate disease progression through osteoclast inhibition or direct anti-tumor[30–35] or anti-angiogenic[36] effects suggested by in vitro studies.

6. Discussion

MBP remains one of the most significant causes of morbidity among patients with advanced cancer. Bone metastases cause ongoing pain that progresses in severity and becomes constant over time, as well as severe breakthrough pain that can be spontaneous or movement evoked. Current treatment options may be ineffective or cause unacceptable side effects. Experiments using a mouse model suggest that MBP is caused by multiple mechanisms. Because of this, successful palliation of MBP may require therapies that act via different mechanisms at different stages of disease. All tumor types metastasizing to bone induce bone destruction through activation of osteoclasts, which can cause MBP through bone destabilization, sensory neuron destruction, and the generation of acidosis. Initial studies suggest that bisphosphonates, which inhibit osteoclast activation, may represent an important therapeutic option for MBP. Murine studies with ibandronate in MBP are under way, including studies of intensive loading-dose treatment for pain relief. These may also determine whether ibandronate can attenuate disease progression, which would have important clinical implications. Overall, murine studies have revealed an important information on the specific mechanisms that cause MBP. Further study is needed to increase the current understanding and to translate experimental findings into improved treatment options for patients with advanced cancer.

Conflict of interest statement

The author has served as a consultant to Roche.

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REFERENCES

1. Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain* 1997;**69**(1–2):1–18.
2. Bonica JJ. Management of cancer pain. *Acta Anaesthesiol Scand Suppl* 1982;**74**:75–82.
3. Urch C. The pathophysiology of cancer-induced bone pain: current understanding. *Palliat Med* 2004;**18**(4):267–74.
4. Mercadante S, Arcuri E. Breakthrough pain in cancer patients: pathophysiology and treatment. *Cancer Treat Rev* 1998;**24**(6):425–32.
5. Mercadante S, Radbruch L, Caraceni A, et al. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. *Cancer* 2002;**94**(3):832–9.
6. Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. *Pain* 1995;**63**(1):65–76.
7. Mercadante S, Fulfaro F. World Health Organization guidelines for cancer pain: a reappraisal. *Ann Oncol* 2005;**16**(Suppl. 4):iv132–5.
8. Cherny N, Ripamonti C, Pereira J, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001;**19**(9):2542–54.
9. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain* 2003;**4**(5):231–56.
10. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer* 2002;**2**(8):584–93.
11. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med* 2004;**350**(16):1655–64.

12. Coleman RE, Major P, Lipton A, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol* 2005;**23**(22):4925–35.
13. Luger NM, Mach DB, Sevcik MA, Mantyh PW. Bone cancer pain: from model to mechanism to therapy. *J Pain Symptom Manage* 2005;**29**(Suppl. 5):S32–46.
14. Mantyh PW, Clohisy DR, Koltzenburg M, Hunt SP. Molecular mechanisms of cancer pain. *Nat Rev Cancer* 2002;**2**(3):201–9.
15. Sabino MA, Mantyh PW. Pathophysiology of bone cancer pain. *J Support Oncol* 2005;**3**(1):15–24.
16. Luger NM, Sabino MA, Schwei MJ, et al. Efficacy of systemic morphine suggests a fundamental difference in the mechanisms that generate bone cancer vs inflammatory pain. *Pain* 2002;**99**(3):397–406.
17. Sevcik MA, Luger NM, Mach DB, et al. Bone cancer pain: the effects of the bisphosphonate alendronate on pain, skeletal remodeling, tumor growth and tumor necrosis. *Pain* 2004;**111**(1–2):169–80.
18. Luger NM, Honore P, Sabino MA, et al. Osteoprotegerin diminishes advanced bone cancer pain. *Cancer Res* 2001;**61**(10):4038–47.
19. Honore P, Luger NM, Sabino MA, et al. Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain and pain-related neurochemical reorganization of the spinal cord. *Nat Med* 2000;**6**(5):521–8.
20. Sabino MA, Ghilardi JR, Jongen JL, et al. Simultaneous reduction in cancer pain, bone destruction, and tumor growth by selective inhibition of cyclooxygenase-2. *Cancer Res* 2002;**62**(24):7343–9.
21. Conte PF, Latreille J, Mauriac L, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. *J Clin Oncol* 1996;**14**(9):2552–9.
22. Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. *J Clin Oncol* 1999;**17**(3):846–54.
23. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. *J Clin Oncol* 1998;**16**(6):2038–44.
24. 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**(15):3314–21.
25. Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases (Corrigendum published in Ann Oncol 2004;15:180). *Ann Oncol* 2003;**14**(9):1399–405.
26. Body JJ, Diel IJ, Bell R, et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. *Pain* 2004;**111**(3):306–12.
27. Diel IJ, Body JJ, Lichinitser MR, et al. 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**(11):1704–12.
28. Heidenreich A, Ohlmann C, Olbert P, Hegele A. High-dose ibandronate is effective and well tolerated in the treatment of pain and hypercalcaemia due to metastatic urologic cancer. *Eur J Cancer* 2003;**1**(Suppl. 5):S270. (abstract 897).
29. Mancini I, Dumon JC, 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**(17):3587–92.
30. Fromigue O, Lagneaux L, Body JJ. Bisphosphonates induce breast cancer cell death in vitro. *J Bone Miner Res* 2000;**15**(11):2211–21.
31. Hiraga T, Williams PJ, Mundy GR, Yoneda T. The bisphosphonate ibandronate promotes apoptosis in MDA-MB-231 human breast cancer cells in bone metastases. *Cancer Res* 2001;**61**(11):4418–24.
32. Dumon JC, Journe F, Kheddoumi N, Lagneaux L, Body JJ. Cytostatic and apoptotic effects of bisphosphonates on prostate cancer cells. *Eur Urol* 2004;**45**(4):521–8.
33. van der Pluijm G, Vloedgraven H, van Beek E, van der Wee-Pals L, Lowik C, Papapoulos S. Bisphosphonates inhibit the adhesion of breast cancer cells to bone matrices in vitro. *J Clin Invest* 1996;**98**(3):698–705.
34. Boissier S, Magnetto S, Frappart L, et al. Bisphosphonates inhibit prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrices. *Cancer Res* 1997;**57**(18):3890–4.
35. 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**(11):2949–54.
36. Fournier P, Boissier S, Filleur S, et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res* 2002;**62**(22):6538–44.
37. Schwei MJ, Honore P, Rogers SD, et al. Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain. *J Neurosci* 1999;**19**(24):10886–97.