J Musculoskel Neuron Interact 2002; 2(6):561-562

Mini-Review Article

Hylonome

The involvement of prostaglandins in tumorigenesis, tumor-induced osteolysis and bone cancer pain

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Keywords: Bone Destruction, Metastasis, Sensitization, Spinal Cord, Hyperalgesia, Cyclooxygenase-2

The abbreviation used, COX-2 = cyclooxygenase 2

Bone and bone cancer pain are one of the most difficult of all persistent pain states to fully control. Common sequels of malignant tumors in bone include severe pain, skeletal fractures, bone marrow suppression, hypercalcemia and an overall reduced quality of life[1]. Skeletal pain is the most frequent indication that sarcomas are present in bone; bone metastases are the most common indication that breast, prostate, or lung cancers have spread beyond the primary organ; and metastases of these tumors to bone are generally associated with a poor prognosis[2]. Moreover, pain is the most frequent presenting symptom indicating tumor metastasis to bone[3].

In general, there are two types of pain in patients with bone cancer. The first type is known as ongoing pain and is usually described as a dull aching or throbbing pain that increases in severity over time[3]. A second type of bone cancer pain, known as movement-evoked, breakthrough, or episodic pain, frequently emerges over time, is more acute in nature and often occurs as spontaneous and intermittent exacerbations of pain or by movement of the cancerous bone[4]. Breakthrough pain represents one of the most serious and highly debilitating complications of cancer as it frequently can be difficult to effectively manage.

The mechanisms which underlie tumor-induced bone cancer pain have only begun to be elucidated. Previously, we developed an animal model of bone cancer pain by injecting osteolytic murine sarcoma cells into the mouse femur[5]. Using this model we demonstrated that blocking tumor-induced bone resorption resulted in a reduction in ongoing and movement-evoked pain behaviors, as well as spinal neurochemical changes reflecting both peripheral and central sensitization[6,7]. While this and other work suggests that tumor-induced bone resorption plays a role in driving bone cancer pain, other mechanisms, such as the release of pronociceptive compounds (e.g., prostaglandins) by tumor and/or inflammatory cells may also be involved[8].

Several tumor types including sarcomas and breast, prostate, and lung carcinomas grow in or preferentially metastasize to the skeleton where they proliferate and induce significant bone remodeling, bone destruction and cancer pain. Many of these tumors, as well as sensory and spinal cord neurons, express the isoenzyme cyclooxygenase-2 (COX-2) which is involved in the synthesis of prostaglandins. To begin to define the role prostaglandins play in driving bone cancer, bone remodeling and bone cancer pain, we used an *in vivo* model where murine osteolytic 2472 sarcoma cells, which were stably transfected with green fluorescent protein (GFP), were injected and confined to the intramedullary space of the femur of male C3HHeJ mice. Following tumor implantation, mice develop ongoing and movement-evoked bone cancer pain-related behaviors, extensive tumor-induced bone resorption, infiltration of the marrow space by tumor cells, and stereotypic alterations in the spinal cord reflective of a persistent pain state. Thus, following injection of tumor cells, bone destruction is first evident at day 6 and pain-related behaviors are maximal at day 14.

To explore the involvement of COX-2-generated prostaglandins in driving bone cancer and bone cancer pain, a selective COX-2 inhibitor was administered either acutely (NS-398, Sigma, St. Louis, Missouri; 100mg/kg, i.p.) on day 14 or chronically in chow (MF tricyclic, Merck & Co., Kirkland, Quebec; 0.015%, p.o.) from day 6 to day 14 following tumor implantation[10]. Mice were then assessed for behavioral, radiological, immunohistochemical, fluorescent, and histologic indices of bone cancer. Acute administration

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Accepted 1 August 2002

of a selective COX-2 inhibitor attenuated both ongoing and movement-evoked bone cancer pain but did not affect tumor burden or tumor induced bone destruction. In contrast, chronic inhibition of COX-2 significantly reduced ongoing and movement-evoked pain behaviors and reduced tumor burden, osteoclastogenesis and bone destruction by over 50%. The present results suggest that chronic administration of COX-2 blocks prostaglandin synthesis at multiple sites and given their relatively low side effect profile, selective COX-2 inhibitors may have significant clinical utility in the management of bone cancer and bone cancer pain.

References

1. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001; 27:165-176.
2. Braun S, Pantel K, Muller P, Janni W, Hepp F, Kentenich CRM, Gastroph S, Wischnik A, Dimpfl T, Kindermann G, Riethmuller G, Schlimok G. Cytokeratin-positive cells in the bone marrow and survival of patients with stage I, II, or III breast cancer. N Engl J Med 2000; 342:525-533.
3. Mercadante S. Malignant bone pain: pathophysiology and treatment. Pain 1997; 69:1-18.
4. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 1999; 81:129-134.
5. Schwei MJ, Honore P, Rogers SD, Salak-Johnson JL, Finke MP, Ramnaraine ML, Clohisy DR, Mantyh PW. Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain. J Neuroscience 1999; 19:10886-10897.
6. Honore P, Luger NM, Sabino MA, Schwei MJ, Rogers SD, Mach DB, O'Keefe PF, Ramnaraine ML, Clohisy DR, Mantyh PW. Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain and pain-related neurochemical reorganization of the spinal cord. Nat Med 2000; 6:521-528.
7. Luger NM, Honore P, Sabino MAC, Schwei MJ, Rogers SD, Mach DB, Clohisy DR, Mantyh PW. Osteoprotegerin diminishes advanced bone cancer pain. Cancer Res 2001; 61:4038-4047.
8. Payne R. Mechanisms and management of bone pain. Cancer 1997; 80:1608-1613.
9. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Bonventre JV, Woolf CJ. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 200l; 410:471-475.
10. Sabino MA, Ghilardi JR, Jongen JL, Keyser CP, Luger NM, Mach DB, Peters CM, Rogers SD, Schwei MJ, de Felipe C, Mantyh PW. Simultaneous reduction in cancer pain, bone destruction and tumor growth by selective inhibition of cyclooxygenase-2. Cancer Res 2002; (in press).