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Perspective Article

Cancer of the prostate - Implication for bone metastases

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This presentation reviews the theories behind the propensity of prostate cancer to cause bone metastases and skeletal implications of prostate cancer biology and treatment modalities. It also reviews the use of human prostate cancer cell line CWR22 to induce osteoblastic bone changes in using a nude rat model.

Prostate cancer is the second most commonly occurring cancer in American men. The American Cancer Society estimates that approximately 180,000 new prostate cancer patients will be diagnosed with prostate cancer every year in the US. The lifetime risk of developing prostate cancer is about 10 percent, and the risk that men will die of prostate cancer is less than 5 percent[1]. Morbidity and mortality are consequences of bone metastases that occur in approximately half of patients diagnosed with prostate cancer. During the next millennium, as the aged population increases, it is expected that the incidence and mortality of prostate carcinoma will continue to soar.

To metastasize successfully, cancer cells have to detach from the primary tumor, invade blood or lymphatic vessels, travel in the circulation to a distant site and establish a new cellular colony. The growth of the prostate cancer cells is initially androgen-dependent, and therefore androgen ablation therapy has been the most effective treatment for patients with metastatic prostate cancer. However, androgen ablation appears to be effective for only a limited duration of time due to the progression of prostate cancer tumor cells from an androgen-dependent to an androgen-independent state, which in addition to tumor ability to cause osteoblastic bone metastases is the hallmark of disseminated disease.

The escape of tumor cells from the primary tumor in the prostate to secondary tumor sites in the axial skeleton probably occurs before the primary tumor is detected. Several theories offer explanations for the observed proclivity of prostate tumors to selectively colonize axial skeleton[2-10]. The interaction between the tumor cells and cells that populate bone marrow, in particular osteoblasts and osteoclasts, is important for creating a "fertile" environment where tumor cells can establish and grow[4,11,12]. Prostate cancer cells are capable of producing growth factors that can affect both osteoblasts, resulting in osteoblastic bone formation, and osteoclasts, resulting in excessive bone resorption[13-18]. In addition to the capability to progress from testosterone-dependent to testosterone-independent phenotype, the hallmark of metastatic prostate cancer is osteosclerosis similar to one induced experimentally in nude rats using CWR22 human prostate cancer cell line[19-22].

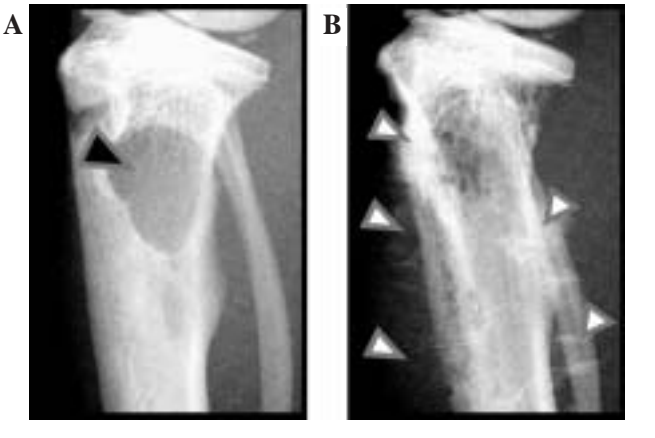

Figure 1: Radiography depicts tibia of the nude rat six weeks following intra-tibial injection with **PC-3** (**A**; osteolytic) and **CWR22** (**B**; osteoblastic) human prostate cancer cell lines. Arrowhead(s) indicate osteolytic and osteoblastic bone response to cancer cells.

Metastatic bone disease caused by excessive bone formation and bone resorption is the major cause of morbidity in patients with prostate cancer[21-23] (Figure 1). The most common symptoms include pain, pathological fractures, spinal cord compression, cranial nerve palsies, bone marrow suppression and hypercalcemia[24,25]. The introduction of prostate specific antigen in clinical practice created a shift where more prostate cancer patients with early disease receive androgen ablation treatment, which in return causes more

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bone loss and cancer associated osteoporosis[26-28]. Introduction of the third generation of bisphosphonates to treat skeletal consequences of malignancy further stressed the important interaction between the bone marrow stroma and cancer cells[29-31]. Animal models and human prostate tumor cell lines that mimic all aspects of skeletal conditions in prostate cancer patients including osteoblastic bone response are highly desirable in order to develop and screen for novel therapeutic and diagnostic modalities.

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