Bone Directed Therapies for Prostate Cancer

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Purpose: Bone is the most common site of metastatic disease in prostate cancer and the lead cause of significant morbidity. Preclinical and clinical studies have provided insight into the pathophysiology of bone metastases and the changes that occur in the bone microenvironment that result in a favorable site of growth for prostate cancer. We provide an overview of recent advances in understanding bone biology, and bone targeted therapy research and development.

Materials and Methods: We reviewed recent research findings related to the biology of bone metastases, approaches to targeting osteoclast function, approaches to targeting osteoblasts and advances in assessing the treatment response to bone targeted therapies in the context of prostate cancer management.

Results: To date targeting some of the key players in the bone microenvironment has not been associated with a significant antitumor effect or with meaningful clinical benefit in phase III randomized trials. A significant limitation in the development of bone targeted therapy has been the inability to objectively assess treatment response. Investigation of improved imaging techniques are ongoing to provide better treatment assessment and, therefore, allow more rapid drug screening and development.

Conclusions: It is our recommendation that future therapy development should be combination based, focusing on simultaneous targeting of multiple relevant pathways. Most important of all is the direct targeting of prostate cancer cells.

Key Words: prostate, prostatic neoplasms, bone and bones, neoplasm metastasis

In 2007 an estimated 27,050 men will die of prostate cancer in the United States.[1] Although patients with nonmetastatic prostate cancer have relatively higher survival rates, patients with metastatic disease do not fare as well. Several novel approaches to treatment are being investigated and they are discussed in other sections of this supplement. We reviewed the rationale and use of bone targeted therapy.

Bone is the most common site of metastatic disease in PCa, affecting 85% to 90% men with metastases,[2,3] and it is a cause of significant morbidity. Preclinical and clinical studies have provided insight into the pathophysiology leading to the development of bone metastases and the changes that occur in the bone microenvironment that result in a favorable site of growth. By exploiting these changes innovative therapeutic approaches have been and continue to be investigated (see Appendix).

Biology of Bone Metastases

Preclinical and clinical studies have uncovered a complicated system of multiple interacting proteins and pathways that contribute to the development of bone metastases.[4–11] The relative role of each is still being investigated, although a general understanding has been established. After prostate cancer cells arrive in bone 4 major players are involved in establishing metastases, including cancer cells, osteoblasts, osteoclasts and mineralized bone matrix, which is a major source of immobilized growth factors. Prostate cancer cells secrete factors that stimulate the osteoblast to proliferate, differentiate and secrete growth factors, which are deposited into the bone matrix and also enrich the local microenvironment of tumor cells (see figure). It is recognized that metastases result from a heterogeneous mixture of osteoblastic and osteolytic lesions.[5,12–14] Histomorphometric evidence indicates that osteoblastic metastases form on trabecular bone at sites of previous osteoclast resorption and such resorption is required for subsequent osteoblastic bone formation.[15,16] These findings suggest that PCa induces bone production through an overall increase in bone remodeling.[6,17–19]

When PCa cells metastasize to bone, they initially induce osteoclastogenesis and bone resorption. RANK, its ligand RANKL and its soluble decoy receptor OPG are essential regulators of this process.[7] RANK-RANKL signaling is required for osteoclast differentiation from hematopoietic cells, activation of mature osteoclasts, osteoclast survival and cross-talk with other ligand receptor pathways affecting bone homeostasis.[6,7] As bone is broken down through osteoclastic activity, a variety of growth factors present in bone are released into the microenvironment, providing fertile soil supporting the further proliferation of prostate cancer cells and promoting osteoblastic activity.[5,20] Differentiation of osteoblasts is regulated by many factors. Some of the better described factors are bone morphogenic proteins, ETs, transforming growth factor-β, fibroblast growth factors,

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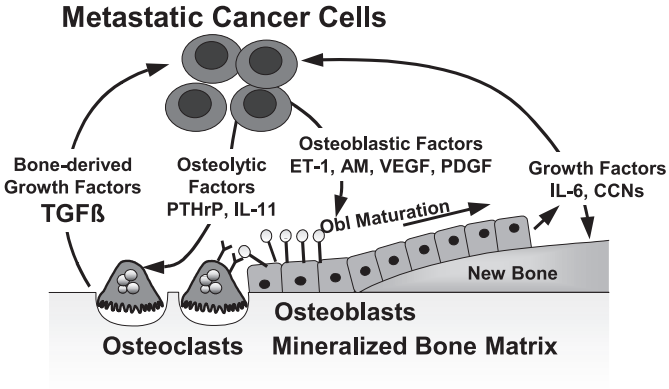

Vicious cycle of prostate cancer cells and bone

platelet derived growth factors, insulin-like growth factors and their receptors.[21] Additionally, other proteins work indirectly to enhance bone production, including PSA, urinary plasminogen activator, serine proteases and parathyroid hormone related proteins.[5] Eventually osteoblast mediated bone mineralization outweighs osteoclast mediated bone resorption, resulting in a predominance of osteoblastic lesions.[5] However, unlike normal lamellar bone, which is composed of collagen bundles that are organized in tightly packed linear fashion, increased osteoblast activity in PCa results in the production of woven bone, which is composed of loosely packed, randomly oriented collagen bundles with suboptimal strength. The combination of increased osteolysis and the production of woven bone leads to the bone complications commonly seen in PCa.[5,22] Targeting PCa induced dysregulation of bone turnover by focusing on the osteoclast and osteoblast has led to several therapeutic approaches.

Targeting Osteoclast Function

Several commercially available and investigational drugs that inhibit the function of osteoclasts directly or indirectly, resulting in decreased bone resorption, are in different stages of investigation for the treatment and prevention of skeletal complications. Predominantly being explored in the osteoporosis arena, many of these drugs are also of interest for treating bone metastases, given the importance of osteoclasts in metastasis development.

Bisphosphonates

Bisphosphonates are analogues of pyrophosphate, a normal constituent of bone matrix, which binds to hydroxyapatite crystals of bone, making them less available for osteoclast resorption.[23] Bisphosphonates also decrease the life span of osteoclasts by promoting their apoptosis, ultimately resulting in decreased bone resorption.[23] Zometa 039 was the first trial to demonstrate a role for bisphosphonates in the treatment of metastatic PCa.[24,25] In this phase III trial 643 men with asymptomatic or minimally symptomatic HRPCa and evidence of bone metastases were randomized to zoledronic acid or placebo. At 15 months patients treated with zoledronic acid experienced fewer SREs, as defined by pathological fracture, spinal cord compression, surgery or radiation therapy to bone, or change in antineoplastic treatment for bone pain (33% vs 44%, $p = 0.02$). Results of this study led to Food and Drug Administration approval of zoledronic acid in patients with HRPCa and evidence of bone metastases. Investigations of other bisphosphonates at different PCa stages has been disappointing as single agents and in combination with hormones and chemotherapy, and they currently have no role in standard treatment for PCa (see table).

The role of zoledronic acid in earlier stage disease has not been clearly defined. Zoledronic acid has been shown to increase bone mineral density and suppress bone turnover markers during the first year of treatment in men receiving gonadotropin releasing hormone agonists when given every 3 months[26] and as a 1 time dose.[27] However, trials of clodronate and zoledronic acid for preventing bone metastases have been negative.[28,29] The completion of additional stud-

Completed phase III studies of bisphosphonates for PCa

Trial	Regimen	No. Pts	Population	Primary End Point	Outcome
Zometa 039[24,25]	Zoledronic acid vs placebo (all pts continued hormone therapy, additional antineoplastics permitted)	643	Androgen independent prostate cancer with asymptomatic or minimally symptomatic bone metastases	Proportion of men experiencing 1 or more SREs by 15 mos	Significant decrease in No. + time to SREs
INT-05/CGP 032[66]	Pamidronate vs placebo (additional hormone therapy + chemotherapy were permitted)	350	Androgen independent prostate cancer with symptomatic bone metastases	Decreased bone pain + narcotic use	No significant difference in pain, analgesic use or SREs
Zometa 704[29]	Zoledronic acid vs placebo (gonadotropic hormone-releasing hormone agonists were continued, additional therapy at investigator discretion)	398	Progressive castrate, nonmetastatic	Time to first bone metastasis	Study was terminated early due to lower than expected event rate
MRC Pr05[67]	Clodronate vs placebo (standard hormone therapy was continued)	311	Androgen dependent, asymptomatic bone metastases	Symptomatic bone progression-free survival	Nonsignificant trend toward improved bone progression-free survival
MRC Pr04[28]	Clodronate vs placebo (standard hormone therapy was continued)	508	Standard treatment for stage T2–T4 disease with no evidence of bone metastases	Time to symptomatic bone metastases or PCa death	No significant difference in time to symptomatic bone metastases or overall survival