INTRODUCTION

Both prostate cancer and treatments for prostate cancer have potentially harmful effects on bone. Prostate cancer reliably metastasizes to bone in its advanced stages, and these metastatic deposits have a variety of deleterious effects on patients including pain and pathologic fractures. In addition, commonly utilized androgen deprivation strategies used in prostate cancer treatment reduce bone mineral density, which in turn can lead to osteopenia or osteoporosis with its attendant risks. Thus, a relatively unique series of relationships exists in prostate cancer patients among the bone, the cancer, and commonly administered treatments.

Although bone metastasis occurs in a variety of human solid tumors, several aspects related to these metastases are relatively unique to patients with prostate cancer. First, the frequency of clinically significant metastases to bone in patients with advanced prostate cancer is exceptionally high. Second, the ratio of soft tissue to bone metastases is exceptionally low. Third, the survival of patients with bone metastases and prostate cancer is relatively prolonged compared with that of patients with bone metastases from other common solid tumors such as lung cancer. As a consequence, the prevalence of this condition is high compared with that of other malignant conditions. Fourth, metastatic prostate cancer is remarkably osteoblastic compared with the lesions caused by most other metastatic tumors.

This chapter focuses attention on two broad methods of therapeutically targeting bone metastases in prostate cancer patients. These include the bone-seeking radioisotopes and the bisphosphonates. This is not to say that other therapies are not applicable to the treatment of bone metastases in prostate cancer patients; quite clearly external beam radiation and a variety of systemic therapies (including hormonal therapy and chemotherapy) may play an important therapeutic role in these patients. However, as these therapies are not bone targeted, they are not covered in this chapter. Because androgen deprivation therapies induce osteoporosis, aspects related to this therapy-induced condition are covered as well.
THE PATHOPHYSIOLOGY OF BONE METASTASIS

Studies of venous blood samples in prostate cancer patients reveal that cytokeratin and prostate-specific antigen (PSA) mRNA-expressing cells can be detected in a substantial percentage of cases (1–3). These results imply that circulating prostate cancer cells are common in men with prostate cancer. Despite this finding, which implies that virtually all organs will be seeded with prostate cancer cells, overt metastases are restricted to bone in approx 80% of cases in patients with advanced prostate cancer (4–7). This provides validation for the “seed and soil” hypothesis of metastatic disease originally proposed by Paget in 1889 (8). Also providing evidence in support of this hypothesis is the finding that careful examination of autopsy materials in patients with advanced prostate cancer indicates that microscopic metastases are widespread (particularly in the lung) but that macroscopic lesions are relatively uncommon outside of the bone (6).

It has long been known that hematopoietic precursors “home” to bone marrow by virtue of cellular interactions between various soluble and insoluble factors. Cytokines and their receptors, various matrix proteins and their receptors, and cell/cell interactions have all been implicated in this process (9,10). It is now assumed that interactions between various receptors expressed on prostate cancer cell receptors and the bone stroma/bone matrix/bone vasculature are necessary for the development of bone metastases. The precise ligand/receptor systems involved with the homing and growth of prostate cancer bone metastases are under current study in various laboratories.

It is known that bone marrow stromal cells, unlike the stroma derived from a number of other tissues, are distinctly supportive of prostate cancer growth (10,11). Thus stromal/epithelial interactions are thought to be central to the fertile “soil” hypothesis. The CXCR4 receptor and its ligands stromal-derived factor-1A (SDF-1A or CXCL12) have been implicated by some investigators in “homing” responses of a variety of cells including prostate cancer (9). Bone matrix proteins such as osteopontin and osteonectin may also play a critical role as these ligands interact with integrins on the cell surface of prostate cancer cells and promote a variety of malignant processes including migration, invasion, and protease activation (12,13). Direct cell-cell interactions may or may not be important in the metastatic process, but it is known that gap junctional communication can be established between stroma and epithelial cells and that communication can be established via this mechanism (14). In addition it is known that stroma and epithelial cells may also have various interactions via cell surface molecules (15). Which of these interactions, or combination of interactions, are most important in establishing clinically relevant metastases is an area of active and ongoing investigation.

As noted above, the osteoblastic nature of prostate cancer bone metastases is also a unique feature of this disease. Although numerous metastatic cancers may cause osteoblastic reactions in bone, none do so as frequently as prostate cancer. Multiple hypotheses have been constructed to explain this observation. Prostate cancer cells are known to secrete various factors that stimulate bone growth. Table 1 briefly summarizes the factors involved in the regulation of osteoblast and osteoclast function and potentially related to prostate cancer bone metastases. One such group, bone-morphogenetic proteins (BMPs) are members of the transforming growth factor-β (TGF-β) superfamily. These proteins, including BMP-1–BMP-7, regulate integrin expression and, as a consequence, cell adhesion. Normal human prostate and neoplastic human prostate cell lines