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Biology and clinical management of prostate cancer bone metastasis

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1. ABSTRACT

Prostate cancer is the most common cancer among men in the United States. Advanced prostate cancer has a particular propensity to metastasize to bone, where it produces predominantly osteoblastic lesions and local bone formation. The tropism for bone is thought to be due in part to specific interactions between the prostate cancer cells and cells present in the bone environment, particularly the bone marrow endothelial cells and osteoblasts. Such interactions involve numerous signaling pathways that could serve as targets for new therapeutic agents. Because androgen directly influences the proliferation and metastasis of prostate cancer cells, the current first-line treatment for metastatic prostate cancer is androgen deprivation therapy. Subsequent therapies include chemotherapy and radiation therapy. New molecular therapies are being developed to target specific steps in the metastatic process. However, as yet none of these therapies has radically improved survival. Nonetheless, it is hoped that with better understanding of the biology of the disease, combination therapy that addresses multiple pathways that support the progression of prostate cancer in bone could significantly improve the survival and quality of life of men with prostate cancer.

2. INTRODUCTION

Prostate cancer is the most common malignancy among men, with an expected 234,460 cases being diagnosed in 2006 in the United States (1). Prostate cancer that progresses beyond organ confinement metastasizes most often to bone, where the disease significantly affects patients' quality of life through symptoms such as bone pain, pathological fractures, anemia, and nerve impingement. The incidence of bone metastasis observed in the clinic varies from 5% to 27% depending on the patient's clinical status and treatments received (2). With the advent of prostate-specific antigen (PSA) testing and earlier detection, fewer patients present with metastases at the time of diagnosis (3). However, despite early detection and intervention, disease in many men will still progress to bone metastasis. Autopsy studies of men who died of prostate cancer indicate that between 83% and 90% had evidence of metastasis to bone (4,5). In addition to its negative effects on quality of life, the development of bone metastasis also significantly affects survival—the median survival time for men with metastatic hormone-resistant disease is less than 12 months (6). Although considerable effort has been invested in the development of new treatments for bone metastases from prostate cancer,

clinical trials have yet to show substantial improvements in clinical outcome. In this review, we first describe the clinical characteristics of prostate cancer bone metastasis; review the biological aspects of the metastatic process; and describe current clinical management strategies for metastatic disease.

3. PATHOPHYSIOLOGICAL CHARACTERISTICS

The most common anatomic sites of skeletal metastasis from prostate cancer are the lumbar spine, vertebrae, and pelvis (4). Several theories have been proposed to explain the propensity of prostate cancer to metastasize to bone. According to the hemodynamic theory, the anatomic position of the paravertebral venous plexus facilitates the movement of prostate cancer cells along veins and lymphatic channels that run upward from prostate to the spine (7,8). Other common sites of prostate cancer metastasis include the sternum, ribs, humeri, and femurs (9). Metastases to the distal extremities (radius, tibia, carpus, tarsus, and phalanges) are relatively rare.

One of the hallmarks of bone metastases from prostate cancer is their osteoblastic (bone-forming) appearance, with radiography usually showing dense mineral deposition at the metastatic sites. In most cases, lesions are osteoblastic (65%) or mixed osteoblastic-osteolytic (23%); osteolytic (bone-lysing) lesions account for only 12% of cases (10). Histologic analysis indicates that most metastatic tumors are located in the bone marrow, suggesting that the interactions between the tumor cells and cells in the bone microenvironment, particularly osteoblasts and osteoclasts, occur at the endosteal interface (11). Osteoblastic or osteolytic responses are reflected by changes in serum or urinary levels of bone turnover markers such as bone-specific alkaline phosphatase (12,13) or type I procollagen C-propeptide for bone formation, and type I collagen cross-linked C-telopeptide (14) or N-telopeptides of type I collagen (15,16) for bone resorption. Elevated levels of these bone-turnover markers indicate an increase in bone remodeling and possibly the presence of bone metastases.

4. PATHOGENESIS

Two main hypotheses have been proposed to explain the non-random patterns of cancer metastasis. In addition to the hemodynamic theory, the ‘‘seed-and-soil’’ theory was advanced more than a century ago (17). This theory continues to be plausible for explaining the mechanism of attraction to and subsequent growth of disseminated cancer cells (seeds) in a preferential organ or tissue microenvironment (soil) (18). For prostate cancer cells to metastasize to bone, they must go through a multistep process involving dislodgement from a primary site, survival in the circulation, binding to the resident cells in bone, and survival and proliferation in the bone (19). This process requires interactions among the prostate cancer cells, the circulatory system, and the bone microenvironment. The exact cellular and molecular mechanisms underlying the metastasis of prostate cancer to bone have yet to be elucidated; however, the following sections describe the current state of knowledge.

4.1. Circulating tumor cells and bone metastasis

The presence of circulating tumor cells is probably the first indication of prostate cancer dissemination. Circulating prostate cancer cells have been identified in peripheral blood samples (20) and in bone marrow aspirate samples (21) by using immunohistochemical staining or reverse transcriptase–polymerase chain reaction (RT-PCR) techniques to detect markers of prostate epithelium. PSA and glandular kallikrein (hK2) have been detected in bone marrow samples as early as at the first diagnosis of localized disease. Interestingly, PSA is detected about twice as often in bone marrow aspirates than in peripheral blood samples (21), suggesting that more disseminated prostate cancer cells are present in the bone marrow than in the general circulation. Similarly, cytokeratin 18, a marker of prostate epithelium, has also been detected in bone marrow aspirates of men with localized disease (22-24). However, most studies published to date have shown that the detection of the prostate epithelial markers such as PSA and cytokeratin 18 in the peripheral blood or bone marrow of men with prostate cancer before undergoing radical prostatectomy did not correlate with other prognostic criteria (24,25) or with clinical outcome (26-28). However, Shariat and colleagues (29), found that the presence of PSA (detected by RT-PCR) in blood samples collected during the early postoperative period was associated with disease progression. Cells that express PSA or cytokeratin 18 may represent differentiated prostate cancer cells that may not be able to grow and develop into metastatic lesions in bone; other small subpopulations of circulating prostate cancer cells could possess properties similar to stem cells or progenitor cells (described further in section 4.7 below). Undifferentiated cancer cells such as these may not express the PSA protein or other prostate epithelial markers, but they might be able to adapt to and propagate in the bone microenvironment.

4.2. Adhesion molecule–mediated interactions with resident bone cells

If circulating prostate cancer cells are to settle in the bone environment, they must first stop at the sinusoids by adhering to bone marrow endothelial cells (30) and then migrate through the endothelial layer (31). This process involves various adhesion molecules (e.g., selectins, integrins, and cadherins) present on the metastatic prostate cancer cells and on the endothelial cells. Initial docking of the cancer cells to the endothelial cells is likely mediated by cell surface lectin–carbohydrate interactions (30). Subsequent cell adhesion and cell migration are mediated in part by integrin–extracellular matrix interactions, especially those that involve integrin $\alpha_v\beta_3$ as a receptor for vitronectin and osteopontin (32) and integrin $\alpha_2\beta_1$ for type I collegen (33), although many other integrins have also been identified in prostate cancer cells (34). Interestingly, integrin $\alpha_v\beta_3$ can bind selectively to vitronectin or osteopontin depending on the properties of the cancer cells; the binding complexes differentially activate cell migration and phosphatidylinositol-3 kinase/AKT signaling in a

ligand-specific manner (35). Expression of integrin $\alpha_v\beta_3$ in prostate cancer cells can be enhanced by stromal cell-derived factor-1 (SDF-1, also known as CXCL12) (36), which is expressed by endothelial cells, osteoblasts, and some stromal cells; expression of the SDF-1 receptor CXCR4 has been detected in prostate cancer cells (37,38). These observations imply that some bone paracrine factors regulate the expression of adhesion molecules in disseminated prostate cancer cells and promote interactions between the cancer cells and the resident bone cells, thereby contributing to the tropism of circulating prostate cancer cells for bone.

4.3. Survival and proliferation of prostate cancer cells in bone

Upon their arrival at the bone marrow, metastatic prostate cancer cells settle into the bone environment by taking advantage of the rich "soil" there. The noncellular fraction of bone marrow contains many growth factors that may stimulate cancer cell proliferation and enhance their interactions with the resident bone cells. The noncollagenous components of bone, such as osteopontin and osteonectin, also have important roles in cancer metastasis. For example, osteopontin, a ligand for integrin $\alpha_v\beta_3$ (39), has broad functions in cell adhesion, migration, and survival as well as bone remodeling (40-42). Osteopontin levels are usually high in high-grade neoplasia, adenocarcinoma, and metastatic tumors (43). Overexpression of osteopontin by prostate cancer cell lines has been shown to give those cells an advantage in proliferation and invasion (44). Osteonectin (also known as secreted protein rich in cysteine [SPARC]) has also been shown to stimulate prostate cancer cell proliferation (45), invasion (46), and survival (47).

4.4. Osteoblasts and osteoclasts in bone metastasis

In addition to the noncellular fraction of bone marrow, the osteoblasts and osteoclasts are active participants in the survival and proliferation of prostate cancer in the bone compartment through their secretion of growth factors and extracellular-matrix components (48). In normal bone, ongoing bone remodeling is maintained through a dynamic balance in the activities of osteoblasts and osteoclasts. When prostate cancer cells metastasize to bone, that balance is shifted in a way that favors increased bone formation. The increased numbers of osteoblasts often present in the woven bone that forms around the metastatic lesions suggest corresponding increases in osteoblast proliferation and differentiation (49). The increase in the activity of osteoblasts may contribute to the survival and invasiveness of prostate cancer cells by providing abundant extracellular matrices. Although most prostate cancer bone metastases present an osteoblastic phenotype, they also have an underlying osteoclastic component (50,51), as discussed later in this section.

Osteoblast growth and differentiation are regulated by complex signaling, including pathways mediated by growth factors such as bone morphogenetic protein-2, transforming growth factor (TGF)-beta, insulin-like growth factor, fibroblast growth factor, platelet-derived growth factor, endothelin (ET)-1, and Wnt. Many of these growth factors activate a key transcription factor, Cbfa1/RUNX2, in osteoblasts. Prostate cancer cells are thought to secrete factors that affect osteoblast growth and differentiation, resulting in a change in bone homeostasis (48). The role of one such factor, the osteoblast mitogen ET-1 (52), in the osteoblastic metastases characteristic of prostate cancer has been studied extensively (53). In one study, plasma ET-1 levels in men with prostate cancer were found to correlate with cancer progression (54). Studies of atrasentan, an ET_A receptor antagonist, given to men with hormone-refractory prostate cancer showed a modestly suppressive effect on prostate cancer progression in bone (55). These findings support the hypothesis that osteoblasts are involved in prostate cancer bone metastasis.

Other osteoblast-derived factors in addition to growth factors may also contribute to prostate cancer progression in bone. For example, *in vitro* studies have shown that coculturing osteoblasts with prostate cancer cells stimulates the prostate cancer cells to express PSA (56), urokinase-type plasminogen activator (57), and matrix metalloproteinase (MMP) -9 (57). These proteases prompt the release of TGF-beta embedded in the bone matrix (58). TGF-beta and other bone matrix factors in turn enhance the production of ET-1 by cancer cells, which contributes to the proliferation of those cells in the bone marrow. Another important factor produced by osteoblasts is the receptor activator of NF-κB ligand (RANKL), which stimulates cancer cell migration (59). In a murine model of melanoma metastasis, treating mice with the RANKL decoy receptor osteoprotegerin (OPG) prevented the metastasis of melanoma cells to bone, suggesting that RANKL secreted from osteoblasts could have a role in bone metastasis (59).

RANKL also represents a means by which osteoblasts regulate osteoclast activity. Briefly, the binding of RANKL to its receptor RANK on osteoclasts or osteoclast precursors activates osteoclast function, resulting in an increase in bone resorption. OPG, another factor produced by osteoblasts, antagonizes the activity of RANKL. In the process of bone remodeling, elevation of RANKL levels relative to those of OPG favors bone resorption. Prostate cancer cells may also regulate osteoclast activity via osteoblasts; cocultures of prostate cancer cells and primary mouse osteoblasts showed that the cancer cells prompted the osteoblasts to express RANKL and suppressed the expression of OPG (56). More importantly, osteoclast-mediated bone resorption seems to have a role in the initiation of bone metastasis. Evidence from a preclinical animal study suggests that accelerated bone turnover facilitated the metastasis of prostate cancer cells to bone (60), suggesting that increased bone resorption is probably a prerequisite for the successful seeding of the prostate cancer cells in bone.

4.5. Osteomimetic properties of prostate cancer cells

Osteomimicry is another theory proposed to explain the preferential growth of prostate cancer cells in bone. According to this theory, metastatic prostate cancer cells achieve preferential growth in bone by mimicking the behavior of bone cells (61). Animal studies have demonstrated that two LNCaP-derived cell lines (C4-2 and

C4-2B) have higher osteotrophic ability than the parental LNCaP cells (62,63). These two cell-line derivatives also produce relatively high levels of extracellular matrix components like osteopontin, osteocalcin, and bone sialoprotein (61); they also express several osteoblast-related factors like alkaline phosphatase, OPG, and the key osteoblast transcription factor Cbfa1/RUNX2 (64). C4-2B cells also formed osteoblast-like mineralization patterns in *in vitro* cultures (64). The osteomimetic phenomenon has also been observed in human prostate cancer tissues; specifically, metastatic prostate cancer cells were found to express higher levels of RANKL and OPG than did cells in primary tumors or non-osseous metastases (65). These observations suggest that having osteomimetic properties may enhance the survival and propagation of cancer cells in bone microenvironment. How are these bone related genes activated in prostate cancer cells are still not clear. Recent studies by Huang et al. (66,67) have identified β2-microglobin as one of the factors that induce the bone phenotypes or osteomimicry exhibited by prostate cancer cells. They showed that β2-microglobin increased expression of osteocalcin and bone sialoprotein in prostate cancer cell line C4-2B by activating cyclic AMP-responsive element binding protein present in their promoters. Another study by Zayzafoon et al. (68) showed that Notch activation plays a critical role in the ability of C4-2B cells to acquire "osteoblast-like" properties. These factors or their associated pathways could be new therapeutic targets for treatment of prostate cancer bone metastasis.

4.6. Androgen signaling

Most treatment-naïve prostate cancer cells depend on androgen for their survival, and hence androgen-deprivation therapy (ADT) is an important option for halting prostate cancer progression (69). However, the observation that men for whom ADT fails usually are at high risk of developing bone metastases led to the speculation that ADT may change the properties of the prostate cancer cells, the bone environment, or both in a way that could increase the likelihood that hormone-refractory cancer cells would survive and proliferate in bone. The effect of androgen deprivation on prostate cancer cells is still a subject of intensive study (70-72); here, we focus our discussion on the possibility that ADT may modify the bone environment in ways that favor the growth of prostate cancer cells in bone.

Androgen has an anabolic effect on bone growth; it increases trabecular bone formation and reduces osteoclast-mediated bone resorption activity both in humans (73-77) and in animal models (78-80). Androgen action is mediated by the androgen receptor (AR), which is expressed by both osteoblasts and osteoclasts (81). Genetic mutation or deletion of AR in mice results in reduced bone density (82,83), and targeted overexpression of AR in mouse skeletons leads to increased formation of periosteal and trabecular bone (84), suggesting that AR is a critical factor in regulating skeletal homeostasis. Androgen signaling in osteoblasts can be mediated by transcriptional activation of the AR or by non-genomic effects (85,86), but exactly how AR signaling leads to bone growth is not clear. Some findings have implied that androgen modulates RANKL and OPG levels in osteoblasts in a way that inhibits osteoclast activity (74,82,87,88), whereas others suggest that androgen acts directly on osteoclasts by suppressing the osteoclastogenesis induced by factors such as RANKL, macrophage colony-stimulating factor (89), and parathyroid hormone (90). Although accumulating evidence strongly supports the concept that androgen has a direct effect on male bone growth, androgen may also affect bone indirectly via estrogen receptor-mediated signaling, in which testosterone is converted to estradiol by aromatase; this regulatory mechanism is also critical for maintenance of skeletal homeostasis in men (91).

Androgen deficiency, whether resulting from natural aging or clinical intervention, can increase osteoclast-mediated bone resorption and affect the bone microenvironment, which as noted previously may be a prerequisite for the successful seeding of prostate cancer cells in bone and therefore may ultimately increase the risk of bone metastasis. Preventing this putative effect of ADT on bone may require manipulating alternative targets of androgen action, such as AR cofactors (92). The differential distribution of these cofactors according to tissue or cell type may allow new drugs to be developed that selectively modulate androgen activity in prostate epithelial cells but not in resident bone cells.

4.7. Prostate cancer stem cells and bone metastasis

Another theory that has been proposed to explain the behavior of prostate cancer cells, although still largely conceptual, is that of cancer stem cells. Cancer stem cells by definition have the capacity for self-renewal and for generating heterogeneous lineages of cancer cells within tumors (93). The clinical observations of cancer recurrence and the generation of phenotypically heterogeneous cancer foci could be explained by a cancer stem cell model (94). In experimental terms, cancer stem cells should be able to generate continuously growing and evolving tumors in *in vivo* models.

Studying the concept of cancer stem cells requires understanding the properties of normal stem cells. Stem cells, normal or cancerous, have an extensive capacity for self-renewal and can maintain an undifferentiated subpopulation over the lifetime of the host. Stem cells can also differentiate in a variety of ways to generate a variety of cell types according to microenvironmental cues. In adult tissues, only very small numbers of stem cells are present in "niches" or defined microenvironments. In the prostate, the niche is believed to be at the basal layer of the epithelial compartment. Tissue renewal and repair are usually handled by progenitor cells, which are derived from stem cells but still have the potential for further differentiation. A well-known example of normal stem cells is the hematopoietic stem cell and its progenitors (95).

Support for the concept that prostate cancer involves cancer stem cells comes from the results of a rodent castration model (96,97). In that model, surgical androgen depletion causes the loss of highly differentiated secretory epithelial cells and their less differentiated

precursors, resulting in atrophy of the adult prostate. The basal cells, however, survive, and reintroduction of exogenous androgenic steroids can completely restore the prostate cell hierarchy. This castration–rescue cycle can be repeated multiple times. These observations led to the hypothesis that primitive stem cells that are androgen-independent exist in the basal layer. Such cells could give rise to progenitor cells and, under androgen stimulation, differentiate into luminal secretory epithelial cells. In agreement with this hypothesis, a subset of mouse prostate cells enriched for the stem cell antigen-1 (Sca-1) was recently found to be able to regenerate into tubular structures containing basal and luminal cells in a renal capsule reconstitution assay (98). The Sca-1^+ cells clustered in the proximal region of the tubules, where the quiescent cells were located. Castration resulted in enrichment of the Sca-1^+ population. Moreover, in a mouse model in which the tumor suppressor gene *Pten* is perturbed by genetic deletion, Sca-1^+ cells displayed strong tumorigenic potential (99,100).

The origin of cancer stem cells remains unclear. Tumorigenic primitive cells could originate from normal stem cells through genetic modification; they could also be derived from intermediate transit-amplifying cells by gaining the capability for self-renewal through mutations or epigenetic modifications (101). The earliest evidence of the existence of cancer stem cells came from transplantation experiments, which showed that only small subsets of cancer cells were clonogenic and capable of forming new tumors. Stem-cell–like cancer cells were initially isolated from human acute myeloid leukemia cells by their expression of the stem cell marker $CD34^+$ (102); only the $CD34^+$ cells could transfer the original leukemia phenotype to the recipient mice. Similar phenomena were subsequently found with solid tumors from breast (103) and brain (104,105). Prostate cancer stem or progenitor cells have been investigated by isolating cancer cell populations bearing surface markers of normal stem cells such as $\alpha_2\beta_1$ integrin, CD133, Sca-1, CD44, and p63. A recent study showed that $CD44^+/\alpha_2\beta_1^{hi}/CD133^+$ prostate cancer cells have a significant capacity for self-renewal and can regenerate phenotypically mixed cell populations that express markers of differentiated cells such as AR and prostatic acid phosphatase (106). Selection based on CD133 led to estimates that the putative prostate cancer stem cells constitute approximately 0.1% of cells in initial tumor cell pools, regardless of tumor grade and sample origin (106).

Whether prostate cancer stem cells are involved in the progression of prostate cancer in bone has yet to be determined. However, the heterogeneity, recurrence, and drug resistance of prostate cancer bone metastases all seem to support the presence of such cells. Clinical observations suggest that some highly metastatic and phenotypically heterogeneous prostate tumors (e.g., mixed small-cell carcinoma and acinar carcinoma) probably originate from an early lineage of stem cells or progenitor cells, whereas other tumors originating from a later lineage (e.g., pure acinar carcinoma) may exhibit a relatively homogenous phenotype and have limited metastatic potential (94). Identification of the origin of the cancer cells may provide opportunities for improved therapy targeted at eradicating the particular subtype(s) of disease present in a given patient.

5. CLINICAL MANAGEMENT

Despite substantial progress in understanding the biology of prostate cancer bone metastasis and the constant development of new therapeutic agents, treatments so far have had only modest effects on patient survival. Currently, management of advanced prostate cancer is mainly palliative, aiming to relieve pain, improve mobility, and prevent bone complications. The main therapies for bone metastasis in most clinical settings are ADT for hormone-sensitive prostate cancer or chemotherapy for hormone-refractory prostate cancer. Additional therapies used as adjuvants include radiotherapy, bone-targeted radioisotopes, and newly developed molecular therapies.

The development of osseous metastases in men with prostate cancer denotes poor prognosis and negatively affects the quality of life of the affected patients. The major factor affecting quality of life is bone pain; other concerns include anemia, nerve compression, and pathological fractures (10). Although bone metastases usually present as new-onset or increasing levels of pain, bone complaints should be interpreted cautiously, because pain alone is not a good indicator of the development of bone metastases (107). The most widely used laboratory marker is serum PSA level. Serologic levels of PSA, a secretory protein whose expression normally depends on androgen signaling, usually reflect the state of prostate cancer cell growth and differentiation. Men with bone metastases usually have high serum PSA levels (i.e., more than 10 ng/ml) and high serum alkaline phosphatase levels. Normal PSA levels, however, do not rule out the presence of metastases. The radionuclide bone scan remains one of the most useful tools for diagnosing bone metastasis.

The sections that follow outline past, current, and future treatment strategies for prostate cancer that has metastasized to the bone.

5.1. Hormonal therapy

Prostate cancer cells express AR and require androgens, secreted predominantly by the testes and adrenals, for survival. Androgens affect not only the growth of prostate cancer cells in the primary tumor but also the progression of tumor cells in bone. In 1941, Huggins suggested that hormonal changes induced by castration and androgen manipulation could alleviate metastatic bone pain (108,109). The main benefit of ADT has been the relief, in most patients, of bone pain, but its effects on survival remain modest (21,110). Androgen depletion can be accomplished surgically by bilateral orchiectomy or pharmacologically by administration of gonadotropin-releasing hormone agonists. The American Society of Clinical Oncology recommends using either one of these methods as first-line ADT (111). Another method of ADT is complete androgen blockade, which involves either of the previous two methods plus an antiandrogen drug, such

as flutamide (112), bicalutamide (113), or nilutamide (114), which function as AR antagonists, to further reduce androgen activity. Other options for hormone therapy include ketoconazole (115,116) and glucocorticoids (117,118). Ketoconazole inhibits cytochrome P450, a key enzyme in the biosynthesis of testosterone precursors through conversion of lanosterol to cholesterol; the antitumor activity of glucocorticoids comes from suppression of androgen secretion, modulation of paracrine/autocrine factors, and perhaps competitive inhibition of androgen-dependent transcription. Androgen deprivation can also be achieved through the administration of estrogen. Most of the estrogen-related studies conducted so far have focused on diethylstilbestrol, which has been shown to be as effective as orchiectomy (119) or gonadotropin-releasing hormone agonists (120). Its safety profile, however, was a major concern owing to the increased risks of cardiovascular-related deaths and strokes in a population already at risk for thromboembolic events (121). With the development of drugs with safer profiles, diethylstilbestrol has fallen out of favor and is now rarely used for this purpose in the United States.

Although 80% to 90% of men with bone metastases from prostate cancer respond initially to hormonal therapy, in most cases the disease develops resistance and advances to a hormone-refractory stage (122). Androgen resistance is thought to be driven by the increasing sensitivity or decreasing specificity to ligand of the AR, which becomes "super-responsive" to even minimal levels of androgen (123). Possible mechanisms for this effect include *AR* gene amplification or mutations or changes in AR cofactor profiles. Although complete androgen blockade would be expected to inhibit the effects of adrenal androgens and thus improve survival rates, clinical trials so far have yielded mixed results (124,125). Because hormonal therapy has fewer side effects than chemotherapy, men who are not experiencing symptoms can safely be given at least one trial of second-line hormonal therapy before proceeding to chemotherapy.

5.2. Chemotherapy

Ultimately, hormonal therapy fails for most patients, requiring alternative therapies. The development of hormone-resistant prostate cancer and the appearance of bone metastases confer a poor prognosis. At this stage of disease, systemic chemotherapy is considered the next therapeutic option. Earlier chemotherapeutic regimens such as mitoxantrone and prednisone did not affect survival (126). In 2004, two important phase III trials showed a survival benefit from use of the taxane docetaxel (Taxotere) (127,128). Docetaxel binds to free tubulin, promoting the assembly of stable microtubules while concurrently inhibiting their disassembly; the net effect is inhibition of tumor cell division. In these trials, men with hormone-refractory prostate cancer had modestly longer survival times after treatment with docetaxel plus prednisone (median, 18.9 months) than did men treated with mitoxantrone and prednisone (median, 16.5 months). Docetaxel and prednisone is now the standard of care in chemotherapy for hormone-refractory prostate cancer. Other phase III trials are underway to study the benefits of combining docetaxel with calcitriol (the "ASCENT-2" trial), atrasentan, or bevacizumab. Although early results have been encouraging, survival benefits thus far remain quite modest, and more effective alternatives continue to be sought.

5.3. Radiation therapy and bone-homing radioisotopes

Radiation therapy can be useful as a supplementary treatment for bone metastases (129). Irradiation is thought to reduce tumor load by inducing apoptosis of tumor cells; it also has a palliative role by decreasing bony pain and may also modify the bone microenvironment so as to render the "soil" less suitable for prostate cancer cell growth. Because prostate cancer cells interact with the cells present in the bone environment (e.g., endothelial cells and osteoblasts), changes in the microenvironment induced by radiation may act to slow the growth of metastatic prostate cancer cells in bone. Local-field radiation, such as focal external-beam radiation therapy, is typically used when one or few localized bone metastases are present (130), but these techniques are of limited benefit for multifocal or diffuse metastatic lesions.

For diffuse metastases, bone-homing radioisotopes, which bind preferentially to osteoblastic bone metastases, are recommended for the treatment. Among the many isotopes available for this purpose [e.g., phosphorus-32 (^{32}P), rhenium-188 (^{188}Rh), strontium-89 (^{89}Sr), and samarium-153 (^{153}Sm)], ^{89}Sr and ^{153}Sm are currently the most commonly used in the United States. Although ^{153}Sm (131,132) or ^{89}Sr (133) can control pain, neither has affected survival time. However, a recent study showed dose-response and survival benefits for patients given repeated doses of ^{188}Rh (134). Only a few studies have considered the potential benefits of combining radioisotopes with chemotherapy. In a phase II randomized clinical trial reported in 2001, men with metastatic prostate cancer that had responded to induction chemotherapy were given doxorubicin with or without ^{89}Sr; those given the ^{89}Sr showed significantly longer survival than those who did not (135). These results suggest the need for targeting both the bone microenvironment and the tumor cells in attempts to improve survival time.

5.4. Bisphosphonates

Bisphosphonates inhibit the activity of osteoclasts either by inhibiting the enzyme farnesyl pyrophosphate synthase or by forming ATP analogues that inhibit ADP/ATP translocase in osteoclast mitochondria. Bisphosphonates have been shown to increase bone density and decrease the incidence of skeletal-related events in women with osteolytic metastases from breast cancer (136). In the treatment of prostate cancer, bisphosphonates are used mainly to prevent the bone loss induced by hormonal therapy and to prevent or reduce skeletal-related events.

ADT increases bone loss and hence results in osteoporosis and a higher risk of fractures (137,138). In one study, giving men with hormone-sensitive prostate cancer and bone metastases zoledronic acid along with the ADT helped to control bone loss, as evidenced by increases in bone mineral density and decreases in bone turnover

biomarkers relative to men not given zolendronic acid (139). Bisphosphonates can also reduce the risk of skeletal-related events from prostate cancer bone metastases (140). Among patients with hormone-resistant disease, zoledronic acid significantly reduced the risk of pathological fractures after a follow-up period of 24 months (141,142). Other bisphosphonates such as pamidronate have not shown significant benefits in clinical trials for prostate cancer so far (143). Because bisphosphonates decrease bone destruction, they were also expected to control bone pain from osteolysis. However, use of zoledronic acid was no more effective than placebo for pain control in one study (142), and pain control was not affected by the addition of clodronate to mitoxantrone and prednisone in another study (144).

Currently, zoledronic acid is the only bisphosphonate approved by the U.S. Food and Drug Administration for the management of prostate cancer and bone metastases that do not respond to hormone therapy. However, the best time to start treatment with bisphosphonate remains unclear. Some investigators have suggested that treatment be started only upon radiographic documentation of osteoporosis (145).

5.5. New targeted and molecular therapies

Increasing understanding of the biological aspects of prostate cancer metastasis is leading to the development of agents that target specific pathways in the metastatic process. Some of these new molecular approaches, which include targeting growth factor pathways, developing peptides that reduce tumor-cell invasiveness, and using immunotherapy and differentiation therapy, are described briefly here. More extensive discussions of these and other therapy approaches can be found elsewhere (146,147).

Agents that block the activity of growth factors implicated in the development of advanced prostate cancer (e.g., ET-1 or vascular endothelial growth factor) are being tested for their effect on bone metastases. ET-1 is highly expressed in men with metastatic prostate cancer (54) and induces proliferation in prostate cancer cells and osteoblasts (148). As noted previously, administration of atrasentan, a selective ET_A receptor antagonist, has been shown to slow the progression of disease, based on serum PSA and alkaline phosphatase levels, in men with metastatic prostate cancer (55,149).

New approaches to inhibiting tumor-cell invasion and metastasis are also being developed. One such strategy involves the development of PHSCN, a peptide that acts to decrease the fibronectin-mediated basement membrane invasion (150). Another strategy involves inhibition of MMPs, which theoretically could be expected to suppress degradation of the extracellular matrix and hence tumor-cell invasion; however, results of clinical trials of peptides developed for this purpose have yet to show any benefit (151).

Immunotherapies that enable recognition and elimination of malignant cells by the immune system are actively being pursued. One method currently under study involves the use of autologous dendritic cells to deliver antigens that stimulate antibody production (152). Another approach involves use of a vaccine created by the transduction and irradiation of prostate cancer cells (153); this approach is based on the idea that overexpression of granulocyte-macrophage colony-stimulating factor by prostate cancer cells could increase the uptake of tumor antigens by the dendritic cells. The vaccine is currently being studied in combination with chemotherapy for men with advanced prostate cancer.

The premise of differentiation therapy is that inducing undifferentiated malignant cells to differentiate would restore normal cell cycling, which in turn may lead to apoptosis. Although differentiation therapy by itself is unlikely to halt the disease, its use is being tested in various combination therapies. Differentiation agents currently being studied include vitamin D (154), histone deacetylase inhibitors such as phenylbutyrate (155), and nonsteroidal anti-inflammatory agents such as cyclo-oxygenase-2 inhibitors (156).

6. PERSPECTIVE

As research continues to reveal the molecular mechanisms of prostate cancer bone metastasis, new therapies that target specific steps involved in this lethal progression are beginning to emerge. However, currently available therapies have resulted in only modest improvements in survival. Effective control of the progression of prostate cancer to bone remains a priority in view of the dismal prognosis of disease at this stage. Logically, one could expect that better disease control could be achieved by combination therapies that address multiple pathways supporting the growth of prostate cancer in bone. The development and clinical implementation of such therapies, however, requires further research on the bidirectional interactions between prostate cancer cells and cells present in bone marrow—bone marrow endothelial cells and osteoblasts in particular. Identification of new factors that facilitate interactions between prostate cancer cells and the bone microenvironment could significantly influence future therapeutic approaches.

The real challenge, however, remains the heterogeneity of prostate cancer, both among patients and between different cancer foci in the same patient. Ultimately, therapy must be highly individualized to be the most effective. As treatment approaches for organ-confined prostate cancer continue to improve, a shift in therapeutic emphasis towards preventing the metastatic spread of prostate cancer to bone will significantly influence the outlook for men with this disease.

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Abbreviations: PSA, prostate-specific antigen; RT-PCR, reverse transcriptase–polymerase chain reaction; SDF-1, stromal cell-derived factor-1; CXCL12, CXC (chemokine with an N-terminal cysteine) ligand 12; CXCR4, CXC receptor 4; TGF-beta, transforming growth factor-beta; ET-1, endothelin-1; MMP-9, matrix metalloproteinase-9; RANKL, receptor activator of NF-κB ligand; OPG, osteoprotegerin; ADT, androgen-deprivation therapy; AR, androgen receptor.

Key words: Prostate Cancer, Metastasis, Bone, Osteoblast, Cancer Stem Cell, PSA, Androgen Deprivation Therapy

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