Management of Advanced/Metastatic Prostate Cancer: 2000 Update

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Over the past several years, the clinical presentation of prostate cancer has evolved so that more patients than ever before are presenting with clinically localized disease. However, a significant number of men continue to

The clinical presentation of prostate cancer has been evolving over the past several years, in part due to increased public awareness of the disease and the availability of prostate-specific antigen (PSA) as a screening serologic test in the late 1980s. Currently, approximately 75% of prostate cancer patients present with clinically localized disease, compared with about 50% in the mid-1980s.[1]

Today, fewer patients with prostate cancer present with an abnormal digital rectal exam. In many current series, the most common category at initial presentation is T1C disease. This represents patients who have elevated serum PSA levels without associated nodularities within the prostate gland on rectal exam but are found to have prostate cancer on biopsy. On the other hand, the incidence of metastatic prostate cancer has almost halved over the past 15 years, so that about 10% to 15% of patients currently present with clinical metastatic disease.

Although both prostate cancer incidence and mortality have begun to decline in recent years, 37,000 men in the United States still died from this disease in 1999, making it the second leading cause of US cancer deaths in men. Invariably, prostate cancer deaths are due to progressive, metastatic disease that has failed initial therapies.

Evolving Biological Principles

Dramatic progress has been made in understanding the molecular and biochemical pathways involved in the development and progression of prostate cancer. Before discussing treatment approaches, we will describe a few examples of the evolving biological principles, which can be grouped broadly into several categories that are not mutually exclusive. Many of the following principles are being incorporated into new treatment strategies.

In terms of normal physiology and malignant transformation, the important interactions between the prostate epithelium and the underlying stroma within the prostate gland are being increasingly recognized.[2,3] Dynamic interactions that normally occur between the stroma, endothelial cells, extracellular matrix, and prostate epithelium can be altered as prostate cancer progresses and metastasizes. Potential alterations in intergrin-mediated cell-cell and cell-extracellular matrix interactions/signaling represent one example.[4]

A family of enzymes called matrix metalloproteases (MMPs), as well as tissue inhibitors of MMPs, are involved in the physiologic remodeling of the extracellular matrix.[5] Perturbations in this remodeling process appear to be an important step in tumor growth and invasion.[5] Formation of new blood vessels is a necessary step for the initial tumors to continue increasing in size and subsequently metastasize.[6] Prostate cancer cells can assume angiogenic potential by secreting growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). In turn, endothelial cells recruited during angiogenesis can stimulate tumor growth by secreting growth factors and cytokines such as interleukin (IL)-1 and IL-6.[6-8]

Changes in Cell Signaling

It is now well recognized that changes in intra- and intercellular signaling response to growth factors,
cytokines, cell-adhesion molecules, and other ligands are a fundamental aspect of tumor pathogenesis. We are now discovering that significant cross-talk can also occur between the various signaling cascades. The erbB family of receptor tyrosine kinases, which mediate signaling functions of epidermal growth factor (EGF)-like growth factors and other ligands (heregulins), are among the most frequently implicated cell surface receptors in human cancers.[9]

HER2—a member of the erbB family of receptor tyrosine kinases—is overexpressed in a proportion of patients with prostate cancer, and presumably contributes to altered cell functions.[10] Although, to date, no direct ligands for HER2 have been found, it appears to modulate signaling via dimerization with other members of the erbB family. Studies suggest that IL-6 signaling in prostate cancer cells via the IL-6 cytokine receptor requires direct interactions of the latter with HER2, thus implicating cross-talk between cytokine receptors and tyrosine kinase receptors.[11]

Androgen-receptor signaling is fundamental to both normal and malignant prostate physiology. Recent work suggests that ligand (ie, androgen)-independent cross-talk can occur between HER2 and androgen receptors during prostate cancer progression.[12] Androgen-independent cross-talk has also been shown to occur between androgen receptors and the protein kinase A (PKA) signal-transduction pathways in prostate cancer cells.[13] In particular, PSA gene expression can be mediated via PKA-dependent phosphorylation of the androgen receptor/coactivator(s) in an androgen-independent manner.[13]

Other Pathways

In addition to examples of the altered cell signaling noted above, other metabolic/biochemical pathways can be modified as a consequence of malignant transformation. In this regard, a key metabolic pathway involving citrate metabolism has been implicated in prostate cancer. Studies have shown that normal as well as benign hyperplastic prostate tissues accumulate very high levels of citrate and zinc.[14] On the other hand, malignant prostate tissue cannot accumulate zinc or citrate.[14]

Although the mechanisms of differential zinc uptake/transport in the normal prostate gland vs prostate cancer have yet to be clarified, recent work has shown that the high levels of zinc in the normal prostate inhibit the enzyme m-aconitase, which prevents citrate from being oxidized, thus resulting in the high citrate levels in the normal prostate. In contrast, the low accumulation of zinc in prostate cancer cannot inhibit m-aconitase, thereby further metabolizing citrate and leading to low levels of citrate in malignant tissue.[14] Metabolic products of arachidonic acid—generated by the action of 12-lipoxygenase—can activate downstream targets like protein kinase C (PKC). These products have been implicated in prostate cancer progression and invasion.[15,16]

Calcium within cells can serve as an important signaling molecule that modulates many cellular processes. For example, a rise in calcium within the cytosol of cells can occur in response to activation of cell surface receptors, and this, in turn, can trigger a variety of biological functions, including muscle contraction, gene transcription, cell-cycle progression, and apoptosis.[17-19]

In prostate cancer, disruption of intracellular calcium homeostasis is a prominent feature of hormone ablative therapy, which remains the cornerstone of treatment for metastatic disease. In particular, androgen deprivation is associated with an increase in cytosolic calcium levels, which normally are tightly regulated. This, in turn, triggers the apoptotic program that results in cell death.[20]

It has been suggested that a failure to generate such an increase in cytosolic calcium in response to hormone ablation may be one of the mechanisms responsible for the hormone-resistant phenotype that often occurs in prostate cancer, resulting in the eventual failure of androgen ablative therapy in this disease.[21] On the other hand, apoptosis can be induced in hormone-insensitive prostate cancer cells if elevated levels of cytosolic calcium can be generated and sustained for several hours.[21]

Genetic Alterations

Ultimately, genetic alterations form the molecular basis for many of the phenotypic changes in cell
biochemistry, cell signaling, and cell-cell interactions that occur as a consequence of malignant transformation. Multiple chromosomal changes have been identified in prostate cancer, and recently, a correlation has been found between tumor grade/tumor invasion and frequency of loss in genetic heterozygosity.[22-24] Examples of genes whose functions may be modified or inactivated during transformation include p53, PTEN, and glutathione S-transferase pi.[25-27]

**Hormone Resistance**

Another important aspect of prostate tumor biology is the emergence of clinical resistance to initial hormone ablative therapy. Although a majority of patients with metastatic prostate cancer respond to androgen deprivation (see below), most ultimately do not, and consequently, hormone-resistant prostate cancer (which is relatively resistant to chemotherapy drugs) emerges.

Whether androgen-dependent and androgen-independent prostate cancer cells are present at the outset, or only androgen-dependent cells are present initially but androgen-independent cells are selected for during hormone ablation, remains an unresolved issue. However, some preclinical models favor the former hypothesis.[28]

Several mechanisms have been implicated in the development of androgen independence, including changes within the androgen receptor and overexpression of the antiapoptotic protein, bcl-2.[29-31] Overexpression and modification of the latter can partly account for the pleiotropic resistance to cytotoxic agents seen in hormone-resistant prostate cancer.

**Evaluation of Response to Treatment**

Evaluating the effectiveness of any cancer therapy requires a definition of parameters that can be used to evaluate response. This has been a particularly difficult problem in advanced prostate cancer, because in a majority of patients with metastasis, the dominant sites of involvement are the bones—which are not readily amenable to the classic criteria of response to therapy. These difficulties are reflected in earlier definitions of response used by the National Prostate Cancer Project (NPCP) in the 1970s, where disease "stabilization" was included in the overall response category.[32]

Ever since PSA screening became available, it has been incorporated in most clinical trials as one marker of disease progression or response to treatment. Several reports have indicated a utility to using a 50% or greater decline in PSA posttherapy as a marker of clinical benefit and possibly prolonged survival.[33,34] However, in most studies, definitions vary regarding the incorporation of PSA as a measure of disease progression or response to therapy. Hence, the Prostate-Specific Antigen (PSA) Working Group recently set a series of guidelines defining (1) the different categories of men with metastatic, androgen-independent prostate cancer who might be eligible for clinical trials; and (2) the criteria of disease progression and response (including changes in PSA) to be used in evaluating patients in trials.[35]

Several investigators have sounded a note of caution, however, with respect to using PSA as a marker of response: Some of the newer, "nontraditional" therapies in current clinical testing (including certain differentiation agents, antiangiogenesis drugs, and growth-factor modulators) may actually upregulate PSA gene expression.[36-38] Another aspect regarding the evaluation of therapies is the use of palliative end points, such as quality-of-life (QOL) measures and pain control.[39] These parameters have been incorporated into many of the trials now evaluating the role of chemotherapy in androgen-independent prostate cancer.

**First-Line Therapy**

Since prostate cancer is primarily dependent on androgens for growth, the initial treatment for advanced/metastatic disease continues to be suppression of testicular androgen production. This therapy was originally described by Huggins 60 years ago in the form of surgical castration (ie, bilateral orchietomy), which effectively removes 90% of circulating testosterone from the bloodstream.[39a]
Another way of nonsurgically suppressing testicular androgens is via analogs of gonadotropin-releasing hormones [GnRH]), which have been available since the 1970s.[40] The GnRH analogs (leuprolide [Lupron], goserelin [Zoladex]) are supra-agonists that, upon binding to the luteinizing hormone-releasing hormone (LHRH) receptor within the pituitary gland, cause an initial surge of LH, and thus, testosterone, release. However, the continued receptor occupancy causes internalization, degradation, and desensitization of the LHRH receptor. This, in turn, leads to decreased testicular androgen synthesis, and hence castrate levels of testosterone within 3 to 4 weeks of drug administration.

Due to the more favorable toxicity profile of the GnRH analogs compared to diethylstilbestrol (Stilphostrol), the GnRH analogs despite their expense have become the treatment of choice for achieving medical castration in the United States. Newer long-acting pure antagonists of GnRH (which avoid the initial LH/testosterone surge) are undergoing clinical trials.[41]

Effective nonsurgical castration can also be achieved with estrogens like diethylstilbestrol (administered at 3 to 5 mg/d). However, due to the increased risk of cardiovascular toxicities, this form of therapy has fallen out of favor, at least in the United States.

Approximately 80% of patients with advanced prostate cancer respond initially to either medical or surgical castration. Substantial responses occur in a majority of patients with soft-tissue disease, including normalization of elevated PSA levels in up to 70% of patients as well as stabilization and improvement of bone lesions in a significant proportion. Those with pain resulting from bone metastasis can achieve almost immediate pain relief upon surgical castration.

Although gonadal androgen suppression removes about 90% of circulating testosterone, other androgens (that are primarily adrenally derived) can also potentially exert tumor-promoting effects. Hence, attempts have been made to suppress the action of the remaining circulating androgens via the use of steroidal (cyproterone, megestrol) or nonsteroidal antiandrogens (bicalutamide [Casodex], flutamide [Eulexin], nilutamide [Nilandron]).

Particularly with the availability of the nonsteroidal antiandrogens (which act by blocking the peripheral androgen receptor), substantial effort and resources have been devoted to determining whether total androgen suppression (achieved by medical or surgical castration plus the use of antiandrogens) is better than gonadal androgen suppression with respect to response rates and survival in patients with advanced prostate cancer.[42,43] Despite a plethora of prospective, randomized trials addressing this issue (27 such trials conducted to date), any significant advantages of total androgen suppression over gonadal androgen suppression have not been clearly demonstrated. If any survival advantages are seen with total androgen suppression, they are likely to occur primarily in patients with metastatic disease who have minimal tumor burden.[44]

Peripheral androgen blockade refers to the use of antiandrogens in conjunction with inhibitors of 5-alpha reductase (finasteride [Proscar]), an enzyme that converts testosterone to its more active form of dihydrotestosterone. With this approach, serum testosterone levels are less likely to be suppressed to castrate levels, and therefore, some side effects associated with gonadal androgen suppression/total androgen suppression (ie, hot flashes, osteoporosis, anemia, muscle weakness, and impotence) are likely to be less pronounced.

Although peripheral androgen blockade can provide control of advanced prostate cancer, questions remain regarding its overall efficacy. Recent randomized trials comparing antiandrogen monotherapy with gonadal androgen suppression or total androgen suppression confirm the superiority of the latter approaches with respect to survival in patients with metastatic prostate cancer.[45,46] Therefore, gonadal androgen suppression plus or minus antiandrogen therapy remains the most effective first-line treatment in patients with advanced prostate cancer.

Second-Line Hormonal Therapies

Although a majority of patients with advanced metastatic prostate cancer respond to initial hormone
treatment with gonadal androgen suppression (with or without antiandrogens) for a median of 18 to 24 months, most, if not all, patients subsequently relapse. Over the past several years, we have begun to see evidence that patients who have apparently developed androgen-independent disease, in fact, represent a heterogeneous population that retains varying degrees of continued hormone sensitivity.[47] Thus, in some of these patients, additional therapeutic benefits could potentially be derived, albeit temporarily, with the use of other second-line hormonal treatments.

Kelly and Scher made an important observation in 1993: A fraction of patients who were treated initially with total androgen suppression (gonadal androgen suppression plus flutamide), but who progressed, could still respond by simply withdrawing the flutamide. [48] Subsequently, other antiandrogens, including bicalutamide, nilutamide, cyproterone, megestrol, and diethylstilbestrol, were also shown to produce responses upon their withdrawal at the time of disease progression.[49-51]

The molecular basis for the antiandrogen withdrawal response has not been clearly defined. However, initial work suggests that as patients progress with combined androgen blockade to an androgen-independent state, alterations (including mutations) can potentially occur within the androgen receptor. In turn, the antiandrogen will not inhibit androgen-receptor function, but will instead behave as an agonist for the androgen receptor.[29] Stopping the antiandrogen under these conditions can, therefore, lead to a withdrawal response.

Approximately 20% to 40% of patients who progress on total androgen suppression respond to antiandrogen withdrawal for a duration of 3 to 5 months.[48-51] Thus, it has now become standard practice to stop antiandrogen therapy as a first step in patients progressing on total androgen suppression. Patients are then observed for at least 1 to 2 months to see if a withdrawal response occurs. Those who fail to respond to this maneuver, and those who progress after initial response to withdrawal, are considered for subsequent therapies.

Use of second-line or even third-line hormonal manipulations is an approach to patients progressing on gonadal androgen suppression or total androgen suppression/antiandrogen withdrawal.[47] Bicalutamide, 150 to 200 mg/d, has been used in this setting with variable success (ie, response rates of approximately 20%).[52,53]

In general, patients who have received prior flutamide as part of combined androgen blockade will most likely respond to high-dose bicalutamide. Ketoconazole (Nizoral), a cytochrome P450 inhibitor with direct cytotoxic effects, in combination with hydrocortisone, has achieved responses of up to 60% to 65% in several small series of hormone-refractory prostate cancer (HRPC) patients.[54] In a recent series of 80 HRPC patients analyzed retrospectively, initiating ketoconazole/hydrocortisone when baseline PSA levels were < 10 ng/mL resulted in prolonged responses compared to ketoconazole started at higher baseline PSA values (25 vs 4 months).[55]

Other second-line hormonal therapies include megestrol, glucocorticoids, and diethylstilbestrol. PC-SPES—a mixture of eight herbal compounds with estrogenic activity—has also been evaluated in a small number of HRPC patients as second-line therapy with variable efficacy.[56; E. Small, personal communication, 2000.]

Other Issues Regarding Hormonal Therapies

When to initiate first-line hormonal ablative treatment in advanced/metastatic prostate cancer remains somewhat controversial. The initial Veterans Administration trial carried out several decades ago in patients with metastatic prostate cancer suggested no survival advantage whether treatments were initiated up front or at the time of disease progression.[57] More recently, a large trial by the British Medical Research Council in patients with M0, MX, or M1 disease, revealed a prostate cancer-specific survival advantage primarily in the M0 group (mortality was 54% in M0 and 70% in M1 patients).[58] Looking at the entire group, the overall incidence of complications from obstructive uropathy or skeletal-related events (pathologic fractures and spinal cord compression) was two times higher in the deferred-treatment group.[58] The present trend is to initiate hormone ablation relatively early in the course of disease.
Another unresolved question pertains to the role of continued gonadal androgen suppression at the time of disease progression. This has become an issue primarily because of the advent of LHRH analogs, which allow gonadal androgen suppression to be reversible. Data are conflicting with respect to whether gonadal androgen suppression should be continued when prostate cancer progresses to an androgen-independent state.[59,60] For clinical trials, the consensus guidelines of the PSA Working Group recommend that gonadal androgen suppression be continued while other therapies are being evaluated in HRPC patients.

Since hormone ablative treatment produces significant side effects and is not curative (with most patients invariably progressing to an androgen-independent state), intermittent androgen ablation has been suggested as an alternative approach in patients with metastatic prostate cancer.[61,62] This has become possible with the advent of methods that allow for reversible androgen suppression.

The rationale for intermittent androgen ablation is twofold: (1) Due to a lack of constant, selective pressure, intermittent—in contrast to continuous—androgen suppression may be less likely to select for androgen independence, thereby potentially allowing for a more prolonged overall duration of disease control; and (2) Many of the side effects associated with androgen ablation are likely to improve when patients are taken off androgen suppression during inter-mittent androgen ablation therapy. Initial preclinical and clinical experiences suggest that this is a viable approach.

The overall impact of intermittent vs continuous suppression on metastatic prostate cancer is not known, but is currently being addressed by an ongoing intergroup phase III trial. In general, however, using PSA levels as a guide for response or recurrence, pilot studies suggest that with intermittent androgen ablation therapy, the duration in which a patient can be kept off androgen suppression gradually shortens with sequential cycles of intermittent hormone ablation, until ultimately, an androgen-independent state emerges.

Chemotherapy

Chemotherapy has been extensively evaluated in patients with metastatic prostate cancer who have failed androgen ablation. The initial experience with most single-agent and several combination chemotherapy drugs in HRPC has been disappointing, with response rates ranging from approximately 10% to 20%.[63] However, over the past several years, the role of chemotherapy in metastatic HRPC has been redefined with the use of traditional, newer measures of response (eg, PSA response, QOL parameters). The number of current pilot phase II trials in HRPC attests to the resurgence of interest in chemotherapy as a potentially important component of managing advanced prostate cancer.

An important HRPC trial was a Canadian study comparing the anthracycline-related derivative mitoxantrone (Novantrone) plus prednisone against prednisone alone.[64] Although impact on overall survival was minimal (less than 1 year in either arm), this study represents the first trial in HRPC patients to incorporate QOL parameters as a primary end point. From this perspective, the trial was positive, showing significant pain relief in 29% of patients for a median duration of 43 weeks in the combined arm vs a 12% incidence of pain relief for a median duration of 18 weeks in the prednisone-alone arm.

This Canadian trial was also the first randomized phase III trial to evaluate chemotherapy in HRPC patients. The relative efficacy of the mitoxantrone/steroid combination in HRPC patients, in terms of palliative end points, has been further confirmed by a second recently completed randomized phase III trial sponsored by the Cancer and Leukemia Group B (CALGB).[65] This combination now represents the standard against which other chemotherapy regimens for HRPC should be tested in the phase III setting. A recently launched intergroup phase III study is now comparing the newly described regimen of docetaxel (Taxotere) and estramustine (Emcyt)[66] to the standard mitoxantrone/steroid combination.

Cytotoxic compounds that target the microtubular network and/or the nuclear matrix are also
beginning to show activity in HRPC patients, especially in combination regimens. In this regard, several drugs deserve mention: estramustine (in which an estrogen moiety is covalently linked to nitrogen mustard) not only has estrogenic activity but also interacts with microtubule-associated proteins. As a single agent, estramustine has very modest activity in HRPC, but has shown in vitro synergism with other compounds that (1) destabilize (vinblastine) or stabilize (paclitaxel [Taxol], docetaxel) microtubules; or (2) interact with the nuclear matrix (etoposide).

Phase I/II and phase II trials combining estramustine phosphate with the above compounds have been carried out or are currently in progress.[66-74] Combinations of estramustine and taxanes are particularly attractive in terms of activity in HRPC. Several permutations of estramustine/taxane combinations are being assessed in pilot studies, with estramustine administered orally either continuously or for 14 days, 5 days, or 1 day of each treatment cycle.[66,70-74] Similarly, in many such combinations, the frequency of taxane administration varies (eg, weekly vs every 3 weeks).[66,70-74]

Another observation of taxanes is that as single agents, they appear to have considerable activity in HRPC patients.[75-77] Overall, response rates (including PSA response) reported in recent trials fall in the range of 40% to 60%, with objective responses reported in about 20% to 40% of treated patients. However, in responding patients, response durations are generally on the order of weeks to months, and impact on overall survival appears modest at best. Whether the promising combination of estramustine/docetaxel represents a true advance in HRPC patients can only be determined by a phase III trial, such as the current study noted above.

Pilot studies of various multiple chemotherapy combination regimens are currently underway. Generally, of the several antimetabolite-based regimens tested so far, none seem to have significant activity. Pharmacologic targeting of the microtubular network with taxane-based drug combinations appears more promising.

**Bone Metastasis**

In advanced prostate cancer, spread to the skeleton occurs in a majority of patients, with skeletal metastases being predominantly osteoblastic in nature. Over the past several years, biochemical and histologic studies have shown that abnormal osteoblastic bone formation in prostate cancer can be preceded by osteoclast activation,[78-80] which is a key event in the establishment and growth of bone metastasis.

Osteoclast activation occurs by bone marrow-circulating cancer cells that produce cytokines, growth factors, and prostaglandins. Thus, bone resorption due to osteoclast activation is important not only in classic osteolytic diseases (such as multiple myeloma and breast cancer), but also in prostate cancer. In fact, the values of resorption markers in prostate cancer can be at least as high as those seen in breast cancer.[78] Both osteoblastic and osteoclastic activities are, therefore, a central component of metastatic spread and progression of prostate cancer in bone.

Consequently, an important aspect of managing advanced prostate cancer patients is the treatment of frequent symptoms and complications of bone metastases.

**Radiation Therapy**

External-beam radiation is effective in a majority of patients with symptomatic bone metastasis from a variety of cancers. Currently, the Radiation Therapy Oncology Group (RTOG) is comparing the relative effectiveness of two different doses and schedules of radiation in breast and prostate cancer patients with painful bone metastases (ie, the standard 30 Gy given in 10 fractions vs 8 Gy given in a single dose).

However, the localized nature of the delivery of conventional radiation therapy can limit its use in multiple or widespread metastatic bone lesions. The use of hemibody radiation for diffuse metastasis can be associated with significant, unpredictable toxicity.[81]
Radiopharmaceuticals

Bone-seeking beta-emitter radiopharmaceuticals offer another approach to patients with extensive bone metastasis.[82,83] Strontium-89 (Metastron) and samarium-153-labeled ethylenediaminetetramethylenephosphonic acid (EDTMP) (Quadramet) both of which target osteoblastic bone lesions will be briefly reviewed.

**Strontium-89**: The dynamics of strontium-89 uptake by the skeleton are similar to that of calcium. Strontium-89 is a beta-emitter with a long half-life of 50.5 days. Several studies have demonstrated the usefulness of strontium-89 in painful bone metastasis from prostate cancer.[84,85] In one large randomized study, the frequency of new painful sites in patients receiving strontium-89 was lower than in those receiving local external-beam radiation.[84]

In the Trans-Canada randomized phase III trial, patients were given external radiation with or without adjuvant strontium-89.[85] In those receiving adjuvant strontium-89, the incidence of new pain sites and need for further radiation was lower than in the radiation-only treated group. Pilot trials of strontium-89 in combination with cytotoxic chemotherapy have also been initiated in HRPC patients.[86] Because strontium-89 has beta-emitting properties and preferential bone absorption, its major toxicity is myelosuppression.

**Samarium-153 EDTMP**: Of the several radionuclides available, samarium-153 EDTMP in which samarium-153 is chelated to the phosphonate EDTMP is particularly attractive due to its physical and biological properties.[87,88] It is a beta/gamma-photon emitter whose medium-energy beta-particle emissions allow for delivery of reasonable doses of radiation with relatively short distances of tissue penetration, and whose associated medium-energy gamma-photon emissions allow for scintigraphic imaging.

Moreover, samarium-153 EDTMP has the shortest half-life (1.9 days) of all the radiopharmaceuticals in use, resulting in more predictable, limited myelotoxicity, and lending to possible fractionated dosing schedules. Samarium-153 EDTMP is rapidly taken up by osteoblastic lesions of the skeleton, with the degree of uptake correlating with the number of metastatic bone lesions.[87]

Several studies have evaluated the use of samarium-153 EDTMP in symptomatic bone metastasis.[87,89,90] In one report, 114 patients with painful bone metastases (mostly from prostate or breast cancer primaries) were randomized to receive single doses of 0.5 mCi/kg or 1.0 mCi/kg samarium-153 EDTMP.[78] At 4 weeks, approximately 55% of patients in the 0.5-mCi/kg group and 70% of patients in the 1.0-mCi/kg group appeared to experience some degree of pain relief, with statistical significance achieved only in the 1.0-mCi/kg group when patient-rated efficacy assessments were compared pre- and posttreatment.[89]

In the only published prospective, placebo-controlled, randomized trial in symptomatic bone metastasis from various primary tumors, a single dose of samarium-153 EDTMP, 1.0 mCi/kg (in contrast to 0.5 mCi/kg or placebo), was found to be effective in providing pain relief that persisted until at least week 16.[90]

**Bisphosphonates**

The bisphosphonates are analogs of pyrophosphate, in which replacement of the central oxygen atom by a carbon atom renders the former highly resistant to degradation by endogenous phosphatases. These compounds possess a P-C-P backbone, in which additional substitutions at the R1 and R2 carbon bonds have given rise to a number of clinically important drugs with varying potencies.

Bisphosphonates have an affinity for bone and are potent inhibitors of osteoclastic bone resorption. Newer bisphosphonates, like zoledronate (Zometa), are approximately 4 to 5 logs more potent than first-generation agents, such as etidronate (Didronel) and clodronate, and 2 logs more potent than the second-generation agent pamidronate (Aredia).

In addition to inhibiting osteoclast activation, bisphosphonates appear to have other biological
effects. They can (1) induce apoptosis in human myeloma cell lines[91] as well as macrophage-like cells[92]; (2) inhibit breast and prostate cancer cell adhesion to bone extracellular matrices[93]; and (3) inhibit matrix metalloproteinase 1.[94]

Clinically, the bisphosphonates are effective in treating cancer-induced hypercalcemia and Paget’s disease of bone. They also reduce skeletal morbidity in multiple myeloma and breast cancer, as demonstrated via several randomized trials of oral (first-generation) or intravenous (second-generation) agents.[95,96] In general, intravenous pamidronate appears to provide a greater benefit with respect to skeletal-related events than oral clodronate in myeloma and metastatic breast cancer.

As noted above, histomorphometric and biochemical studies demonstrate that increased bone resorption is a prominent feature in patients with metastatic prostate cancer. Numerous small studies suggest that bisphosphonates may provide pain relief in prostate cancer patients.[97, 98] However, to date, the use of bisphosphonates in metastatic prostate cancer has not been adequately tested in a randomized trial. Accrual has been completed in a large multicenter, double-blind, placebo-controlled trial using pamidronate in HRPC patients. Its primary end point is a reduction in pain-related events, and its secondary end point is a reduction in skeletal-related events.

Zoledronate is the most potent of the clinically tested bisphosphonates. It is 100 to 850 times more active than pamidronate in several in vivo and in vitro systems. Early experience indicates that doses of only 1 to 2 mg are highly effective in treating hypercalcemia of malignancy, and are also beneficial in relieving bone pain.[99]

Moreover, of all the bisphosphonates, zoledronate offers the largest therapeutic ratio in vitro between the desired inhibition of calcium resorption and the unwanted inhibition of bone mineralization (which can predispose to osteoporosis). At present, the efficacy of zoledronate in the clinical setting is being tested via several ongoing trials. Two multicenter trials are evaluating zoledronate in prostate cancer—one in patients with hormone-refractory metastatic disease, and the other in patients who have failed first-line hormonal therapy but have not yet developed clinical bone metastasis. The goal of the latter trial is to determine whether zoledronate can inhibit the development of bone metastasis in this high-risk group.

Newer Approaches in Development

Based on our greater understanding of prostate tumor biology, a multitude of new therapeutic targets can be envisioned. In fact, the number of compounds in active development that target newly identified pathways of tumorigenesis/metastasis may exceed our ability to adequately test them. This problem may be the result of limitations imposed by the availability of resources, including patients. Nevertheless, many such compounds are entering clinical trials.

Antiangiogenesis Therapy

Since angiogenesis is critical to tumor growth and spread, much effort has been devoted to developing antiangiogenesis therapy. For example, VEGF is one of several mitogens that are important in endothelial cell proliferation. A humanized anti-VEGF antibody, as well as a novel compound (SU 5416) that inhibits VEGF-mediated downstream signaling, are currently undergoing clinical testing.[100-102]

The fumagillin derivative TNP-470 can disrupt endothelial cell proliferation by inhibiting type-2 methionine aminopeptidase and, potentially, other targets.[103,104] Other antiangiogenesis agents in development or clinical testing include anti-integrin antibodies, angiostatin/endostatin, and thalidomide (Thalomid).[105-109]

MMP Inhibitors

For metastasis to occur, there must be degradation of the extracellular matrix. As noted earlier, MMPs play an important role in remodeling the extracellular matrix, and therefore, are a potential
target for therapy. Of the more than dozen MMPs identified, MMP2 and MMP9 seem to be particularly important in tumor growth.

Inhibitors of MMP have anti-invasion/antiangiogenesis effects. Several such compounds have been developed and are being actively evaluated in ongoing clinical trials. Included among the MMP inhibitors are batimastat (BB94), marimastat (BB2516), Bay 12-9566, and prinomastat (AG3340).[110-114] A phase III randomized, placebo-controlled, double-blind, multicenter trial in metastatic HRPC patients evaluating mitoxantrone/prednisone with or without AG3340 recently completed accrual and is awaiting analysis.

Tumor Cell-Signaling Inhibitors

Although complex patterns of cell signaling may be initiated in tumors at the cell surface (due in part to cross-talk between various signal-transduction pathways), attempts are being made to inhibit some of these tumor-promoting signaling events. An example of this is the use of trastuzumab (Herceptin, a monoclonal antibody that targets the erbB-2 receptor). Clinical trials are now testing trastuzumab either as a single agent or in combination with cytotoxic drugs.[115]

Another compound in development is ZD-1839 (Iressa), which interferes with erbB-1 (ie, EGF receptor) signaling.[116] Calcium-dependent signaling and intracellular calcium homeostasis are fundamental to both normal and tumor cell biology. Sarcoplasmic/endoplasmic reticulum calcium transport ATPases (SERCAs) are key enzymes involved in regulating cellular calcium homeostasis. As a consequence, these enzymes are important in many cell functions.[117] Disrupting SERCA function by pharmacologic means can induce apoptosis in prostate cancer cells, and therefore, these enzymes are potential targets for therapy.[118]

Thapsigargin is a highly potent inhibitor of SERCA function. Since SERCAs are housekeeping enzymes, systemic delivery of thapsigargin-type drugs could potentially be very toxic. To circumvent this conceivable problem, prodrugs (in which thapsigargin derivatives are linked to specific peptide carriers) are being developed so that thapsigargin can only be released from the carrier by PSA-mediated proteolytic cleavage of the latter.[119,120] Since the enzyme activity of PSA (a serine protease) is limited to the sites where it is secreted, such prodrugs could theoretically be activated only in the vicinity of PSA-secreting prostate cancer cells. Preliminary work with this strategy is ongoing in both in vitro and in vivo models.

Circumventing Resistance Mechanisms

With the identification of some of the molecular mechanisms involved in the development of hormone resistance and chemoresistance, strategies to circumvent these pathways are being evaluated. For instance, overexpression of bcl-2 has been implicated in about two-thirds of patients with HRPC.[31] Pilot trials have been initiated in which cytotoxic drugs are being combined with antisense bcl-2 oligonucleotides in attempts to inhibit bcl-2 function, and therefore, potentially increase the therapeutic efficacy of the cytotoxics.[121]

Along these lines, retinoids, which decrease bcl-2 expression, are also being combined with alpha-interferon and paclitaxel in HRPC patients.[122] The relative efficacy of the taxanes in HRPC may partly be due to their ability to phosphorylate, and hence, possibly inactivate, bcl-2.

Immunotherapy

Finally, immunotherapy and "gene therapy" strategies are in active development for cancer treatment.[123] Immunotherapy approaches include (1) monoclonal antibodies against various targets (like trastuzumab); (2) autologous tumor cells modified genetically with cDNAs encoding cytokines (eg, granulocyte-macrophage colony-stimulating factor [GM-CSF; Leukine]) or other immune costimulatory molecules; (3) dendritic cells transduced with genes encoding tumor antigens or cytokines; (4) dendritic cells pulsed with peptide antigens (eg, PSA, prostate membrane-specific antigen [PMSA] derivatives); (5) recombinant viral vectors (eg, PSA-expressing vaccinia) that can directly infect antigen-presenting cells and stimulate immune responses; and (6) protein/peptide and carbohydrate-derived products (eg, heat-shock protein [hsp], MUC1) admixed with
adjuvants.[115,124-128]

References:


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