Therapeutic Options in Advanced Prostate Cancer: Present and Future

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Current Urology Reports 2007, **8:**53–59
Current Medicine Group LLC ISSN 1527-2737

Patients with advanced prostate cancer now have many treatment options available including first- and second-line hormonal therapy, radiotherapy, bisphosphonate therapy with zoledronic acid, and taxane-based chemotherapy. These options now give clinicians an opportunity to offer their patients symptomatic relief and most importantly improve overall survival. This article reviews the current treatment options available for men with advanced prostate cancer. In addition, novel treatment options under development, including calcitriol, immunotherapies, small molecule inhibitors, and nucleotide-based targeted therapy, are discussed.

Introduction

Treatment options for men with advanced prostate cancer have changed dramatically over the past 10 years. A decade ago, a review of the literature would have revealed only a 9% response rate for single-drug chemotherapy [1]. This led many clinicians at that time to treat patients with metastatic hormone-refractory prostate cancer (HRPC) with a degree of therapeutic nihilism. Recently, the demonstration of a survival benefit for taxane-based chemotherapy in two large phase III studies [2••,3••] has made it increasingly clear that systemic chemotherapy has an important role to play in metastatic HRPC. Although taxane-based therapy has demonstrated improvement in symptoms, quality of life, and survival, there is a pressing need to expand the treatment options to improve outcomes for this patient population.

"Advanced" prostate cancer has been traditionally defined as disease with bony metastasis at presentation. Today, most patients are diagnosed with early disease, and advanced prostate cancer also includes biochemical relapse, as indicated by a rising prostate-specific antigen (PSA) after a failure of local therapy. Patients with advanced prostate cancer now have many treatment options available including first- and second-line hormonal therapy, radiotherapy, bisphosphonate therapy with zoledronic acid, and taxane-based chemotherapy. These options now give clinicians an opportunity to offer their patients symptomatic relief and most importantly improve overall survival.

Although modest advances have been made in the treatment of advanced prostate cancer, it is clear that newer therapies are needed. There have been a substantial number of novel drugs that have recently been developed that show promise in the treatment of patients with prostate cancer when used alone or when combined with current approaches. Calcitriol, novel immunotherapies, small molecule inhibitors, and nucleotide-based targeted therapy are under development and evaluation and are discussed in this review.

Present Therapeutic Options

First- and second-line hormonal therapy

Androgen deprivation therapy (ADT), either by surgical or chemical castration, (first described in 1941) is the mainstay of treatment for metastatic prostate cancer providing control of advanced disease in approximately 80% of men. There are few therapies in the field of oncology for which such consistent, dramatic response occurs with so few significant side effects. The problem is that the response for first-line hormonal therapy is temporary, lasting a median of 18 to 24 months, at which point the cancer grows in an androgen-independent fashion.

The addition of nonsteroidal antiandrogens (bicalutamide, flutamide, and nilutamide) to surgical or medical castration by luteinizing hormone-releasing hormone (LHRH) agonists is termed combined androgen blockade (CAB). An estimate of the benefit of combined therapy with bicalutamide suggests that there is a high probability that CAB provides a survival advantage over castration alone [4]. The benefit is very modest though (5-year survival of 25.4% for CAB vs 23.4% with castration alone) [5] and must be balanced against the increase in side effects and the decrease in quality of life. CAB is an option as either an initial treatment

maneuver or at the time of development of the androgen-independent state.

An initial step after failure of CAB is withdrawal of the antiandrogen drug. Approximately 10 years ago, it was observed that withdrawal of antiandrogen was associated with a PSA response in about 20% of patients. This has been termed the antiandrogen withdrawal syndrome [6]. Although the responses are clinically significant in many cases, they are unfortunately of short duration (2–10 months).

Secondary hormonal manipulations include adrenal androgen inhibitors (ketoconazole and hydrocortisone, aminoglutethimide and hydrocortisone), or estrogenic drugs (cyproterone acetate, megesterol), with PSA response rates ranging between 18% to 80% [6]. The durability of this response however is short, and a survival benefit has not been demonstrated.

Herein, continuing androgen deprivation in the face of development of androgen-independent disease is an unanswered question. The issues are whether men who have been on long-term LHRH analogue treatment will remain castrate after stopping these treatments and if not, whether increases in testosterone will accelerate disease progression. A retrospective analysis has demonstrated a modest survival advantage in patients who continued androgen deprivation once androgen-independent disease developed [7]. Although there is a lack of prospective clinical data, it remains common practice to continue ADT with androgen-independent disease. Whereas many men with HRPC will remain castrate for the rest of their life after stopping LHRH therapy, it is likely that any rises in testosterone above castrate levels will stimulate the growth of "hormone-refractory" but androgen-sensitive cancer.

Radiotherapy

In advanced prostate cancer, bone pain can be effectively palliated by radiotherapy, with overall responses ranging between 85% to 100%. For multiple painful sites, radiopharmaceuticals, such as strontium-89, can be considered but will not treat adjacent soft tissue disease or neurologic compromise. Of note, toxicity of strontium-89 includes dose-dependent thrombocytopenia [8].

Bisphosphonate therapy

Bony metastases are extremely common in advanced prostate cancer and can cause considerable pain and skeletal morbidity. This is further exacerbated by the decrease in bone mineral density observed in patients on long-term androgen deprivation. Bisphosphonates are a class of drugs that inhibit osteoclastic bone destruction. In addition, they have been shown to have an inhibitory effect on prostate cancer metastasis to bone by blocking proteolytic activity of the matrix metalloproteinases, cell adhesion, and possibly cancer cell growth [9].

A recent, phase III, placebo-controlled trial in men with metastatic HRPC demonstrated fewer skeletal complications in men who received zoledronic acid in addition to other anticancer therapies for prostate cancer [10•]. This trial resulted in the approval of zoledronic acid by the US Food and Drug Administration (FDA) for use in patients with HRPC metastatic to bone who have failed at least one regimen of hormonal therapy. It has been approved in other countries for use in any patient with bone metastases, regardless of disease status. Whether to add zoledronic acid for patients with bony metastases who are still hormone-sensitive is unknown, though clinical trials are investigating the issue. In a randomized trial of men who were starting ADT, zoledronic acid administered every 3 months prevented loss of bone mineral density and further, actually increased bone density compared with placebo [11]. It should be noted, however, that aledronate is the only drug that has FDA approval for the treatment of osteoporosis in men.

Patients starting zoledronic acid should be educated about the possible side effects, including an acute-phase reaction with myalgias and fever in up to 25% of patients. These symptoms are mild, less bothersome with each infusion, and can be treated with nonsteroidal anti-inflammatory drugs. Renal function needs to be assessed for initial dosing and subsequently for each administration. Also of concern, albeit a rare complication, is osteonecrosis of the jaw. Good dental hygiene and pretreatment oral examination are thus important to minimize the occurrence of this side effect.

Chemotherapy

Historically, chemotherapy was thought to have minimal clinical efficacy in men with metastatic HRPC. More recently, a role has emerged with a survival benefit for docetaxel-based (Taxotere; Aventis Pharmaceuticals, Bridgewater, NJ) chemotherapy, as demonstrated in the recent, large, phase III TAX327 and Southwest Oncology Group (SWOG) 9916 trials.

TAX327 was the largest phase III, randomized trial yet conducted for metastatic prostate cancer [2••]. In this trial, 1006 patients with metastatic HRPC were randomized to one of three arms: 1) docetaxel at 75 mg/m^2 every 3 weeks plus prednisone at 10 mg/day; 2) docetaxel at 30 mg/m^2 every week plus prednisone at 10 mg/day; or 3) mitoxantrone at 12 mg/m^2 every 3 weeks plus prednisone at 10 mg/day. Patients receiving docetaxel also received dexamethasone premedication. Results demonstrated a statistically significant improvement in overall survival in the every 3-week docetaxel arm (18.9 months for the docetaxel/prednisone arm compared with 16.5 months for the mitoxantrone/prednisone arm). Statistically different survival was not demonstrated for the weekly docetaxel arm. Quality of life was improved in both docetaxel arms compared with mitoxantrone. Compared with the mitoxantrone regimen, the every 3-week docetaxel regimen was also associated with a significantly improved PSA response rate (45% vs 32%) and a significantly improved pain response rate (35% vs 22%). Adverse events in the docetaxel arms were notable for a higher rate of grade

3–4 neutropenia and neutropenic fever in the every 3-week arm (32% vs 22% treated with mitoxantrone and 1.5% treated with docetaxel weekly). Febrile neutropenia and infection were uncommon in all groups however, and there were no septic deaths in the every 3-week docetaxel arm. Treatment overall was generally well-tolerated with rates of completion for the every 3-week docetaxel, weekly docetaxel, and every 3-week mitoxantrone arms of 46%, 35%, and 25%, respectively. Adverse events that led to treatment discontinuation included fatigue, musculoskeletal or nail changes, and sensory neuropathy, as well as infection in the docetaxel group and cardiac dysfunction in the mitoxantrone group.

In the SWOG 9916 trial [3••] 674 patients with metastatic HRPC were randomized to receive either 1) docetaxel at 60 mg/m^2 on day 2 and estramustine at 280 mg three times daily on days 1–5 every 3 weeks or 2) prednisone at 5 mg twice daily plus mitoxantrone at 12 mg/m^2 on day 1 every 3 weeks. As in the TAX327 trial, dexamethasone was used as prophylaxis before docetaxel treatment. The choice to use estramustine in combination with docetaxel in this trial was based on favorable response rates with docetaxel/estramustine combinations in phase II studies. The docetaxel/estramustine arm exhibited a significant improvement in overall survival (median survival 17.5 months for the docetaxel/estramustine compared with 15.6 months for mitoxantrone/prednisone) and a significant 27% increase in progression-free survival. Docetaxel/estramustine was also associated with a significant improvement in PSA response rate (50% vs 27%) and a nonsignificant, better objective response rate (17% vs 11%). Adverse events occurred more frequently in the docetaxel/estramustine arm, but there were no differences in toxic death rates or rates of study discontinuation between treatments. A 15% incidence of cardiovascular and thromboembolic events in the docetaxel/estramustine arm, however, required an interim safety recommendation of low-dose aspirin and warfarin as thromboembolic prophylaxis.

These two studies (TAX327 and SWOG 9916) led to the recent FDA approval of docetaxel administered every 3 weeks plus prednisone for the treatment of metastatic prostate cancer. Because the median overall survival of docetaxel alone in the TAX327 trial (18.9 months for the weekly arm) was similar and actually better than the docetaxel/estramustine arm in the SWOG 9916 trial (17.5 months), it is thought that estramustine offers little additional benefit over single-drug docetaxel. A potential benefit is an improved PSA decline (> 50% PSA decline observed in 50% of patients in SWOG 9916 compared with 45%–48% in TAX327). The additional toxicity of the estramustine combination regimen and unclear clinical benefit likely precludes the use of estramustine in the absence of a large-scale, head-to-head comparison of docetaxel and docetaxel/estramustine combination.

Future Therapeutic Options

Calcitriol

The biologically active form of vitamin D, 1,25-dihydroxycholecalciferol, has been demonstrated to be synergistic with many commonly used chemotherapeutic drugs, producing antitumor activity as measured in laboratory and animal models [12]. DN-101 (Asentar; Novacea, Inc., San Francisco, CA) is a proprietary high-dose formulation of 1,25-dihydroxycholecalciferol and has entered phase III trials. In the phase II trial of 250 patients (Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere [ASCENT]), survival for patients treated with a DN-101/docetaxel combination was 24.5 months compared with 16.4 months for patients treated with a placebo/docetaxel combination [13]. A phase III study (ASCENT-2) investigating DN-101 in combination with docetaxel versus docetaxel in combination with prednisone is enrolling patients with a target enrollment of 900 patients in this multinational study.

Immunotherapy

A number of observations collectively implicate prostate cancer as a favorable target for immunotherapy. In general, prostate cancer has a long natural history with a generally slow progression. This long interval of time provides an opportunity for the induction and potentiation of T–cell-mediated antitumoral immunity. In addition, the prostate itself is predisposed to various inflammatory conditions that can be related to autoimmunity or result from pathogenic infection. Because the host is capable of mounting a significant immune response to prostate tissue under various nonmalignant pathologic conditions, it is reasonable that patient cell-mediated immune responses may actively suppress prostate tumor progression. Further, unlike other vital organs in which tumors arise, the prostate is a relatively dispensable organ and any autoimmunity that may be acquired by immunotherapy would be of little consequence to the patient.

In prostate cancer, several immunotherapeutic strategies have moved forward into clinical development. Vaccine therapy has generated a tremendous amount of excitement, offering an active immune approach to combat malignancy in a targeted manner. Prostate cancer expresses potentially excellent targets (PSA, prostatic acid phosphatase, prostate-specific membrane antigen, prostate stem cell antigen) that enable the development of highly specific vaccines that recognize the tumor without damaging benign tissue. A number of vaccines are in phase III evaluation including APC8015 (Provenge; Dendreon Corp., Seattle, WA; dendritic-cell approach), GVAX (Cell Genesys, Inc., San Francisco, CA; whole-cell vaccine) and Prostvac-VF (Therion Biologics, Cambridge, MA; viral vaccines) and will be discussed. Also discussed in this review are passive immune strategies using monoclonal antibodies with tumor-associated antigen targets, as well as cytokine therapy to stimulate antitumoral T-cell activity.

Dendritic-cell vaccines

APC8015 (Provenge) is an autologous vaccine derived from CD54+ dendritic cells, the major antigen-presenting cells, which are pheresed from individuals and processed with the recombinant fusion protein prostatic acid phosphatase and the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF). Recently, a randomized phase III trial involving 127 patients with metastatic HRPC treated with APC8015 was conducted [14]. Although early data suggested that the vaccine delayed disease progression and improved survival only in the hormone-refractory disease patients with a Gleason score of less than or equal to seven, a more recent update suggests that advantages in progression-free and overall survival have been observed across all grades after 3 years of follow-up (median overall survival 25.9 months for patients assigned to APC8015 compared with 20 months for patients assigned to placebo). Although this is a small study, it has generated enthusiasm that vaccination with dendritic-cell vaccines may improve overall patient survival. This is the only study to date that has demonstrated a survival advantage to an immunotherapeutic approach to prostate cancer. A phase III trial is under way in patients with Gleason scores of less than or equal to seven.

Whole-cell vaccines

GVAX consists of two inactivated allogeneic prostate carcinoma cell lines (PC-3 and LNCaP) that have been genetically modified to secrete GM-CSF. In a phase II study involving 34 patients with metastatic HRPC, GVAX has been demonstrated to lower serum PSA transiently or reduce PSA progression in some patients, as well as extending time to clinical progression [15]. Median survival in this trial was 26 months, historically very favorable. Another phase II study of 80 patients with metastatic HRPC treated at higher doses [16], as well as two phase III trials (one comparing GVAX with docetaxel/prednisone, and one comparing GVAX/docetaxel with docetaxel/prednisone) in men with metastatic HRPC are ongoing.

Viral vaccines

Viral vaccines are designed to stimulate local tissues to express prostate antigen and critical T-cell activation molecules, essentially converting local tissues into in situ vaccines. One such vaccine is Prostvac-VF, which represents two separate vaccine vectors, one based on recombinant vaccinia PSA vaccine in conjunction with T-cell costimulatory molecules (LFA-3, ICAM-1, B7.1) to prime T-cell responses followed by a fowlpox PSA vaccine boost. Prostvac-VF treatment has been shown in a phase I study to induce transient PSA reductions in roughly 15% of treated patients and produced prostate tumor regression/stabilization in four of 23 patients studied [17].

Monoclonal antibodies

Vascular endothelial growth factor (VEGF) is a glycoprotein important in promoting tumor angiogenesis. RhuMAb VEGF (bevacizumab) is a humanized murine monoclonal antibody that neutralizes VEGF activity and has shown promise in HRPC. Based on promising preclinical data, the role of bevacizumab with estramustine and docetaxel in 79 patients with metastatic HRPC was investigated in the CALGB 90006 trial [18]. Early results show that 53% of patients had a partial response and 65% had a greater than 50% decrease in PSA. This regimen was well-tolerated, though there was some increase in thrombosis. When compared with another CALGB triplet trial in which carboplatin was added to estramustine/docetaxel (CALGB 99813) [19], the use of bevacizumab resulted in a post-therapy PSA decline in 58 of 72 (81%) patients versus 68% of the patients treated with the carboplatin regimen, median time to objective disease progression of 9.7 months compared with 8.1, median time to PSA failure of 9.9 versus 9 months, and overall median survival of 21 months compared with 18 months. These results are encouraging, and safety would be enhanced with the elimination of estramustine, especially in light of the evolving data suggesting that estramustine adds little to the overall survival of patients. A phase III trial comparing docetaxel/prednisone ± bevacizumab in men with metastatic HRPC is planned (CALGB 90401).

Cytokines

The systemic use of interferons (IFNs) and tumor necrosis factor-α has been limited due to toxicity at biologically active doses. Systemic GM-CSF, however, has been investigated in both patients with metastatic HRPC resulting in PSA responses in 10 of 22 patients [20] as well as patients with a climbing PSA after local therapy increasing median PSA doubling time from 8.4 months to 15 months [21]. No overall survival benefit has been demonstrated in patients with metastatic HRPC with cytokine therapy to date.

Small molecule inhibitors

ET-A receptor antagonists

Atrasentan (Xinlay; Abbott Laboratories, Abbott Park, IL) is a potent ET-A receptor antagonist and is the most clinically developed drug of this class of drugs for use in prostate cancer. Endothelin-1 and its ET-A receptor have been demonstrated to have multiple effects on cellular physiology and paracrine signaling in prostate cancer. Endothelin-1 is known to influence cell growth via the mitogen-activated protein kinase pathway and is co-mitogenic with additional growth factors such as insulin growth factor-I and II, and it has also been shown to regulate apoptosis, perhaps through its interactions with Bcl-2 and PI3K/Akt pathways [22]. ET-1 has also been shown to be involved in osteoblastic activity and may regulate the development of painful bony metastasis in prostate cancer.

In phase II trials, metastatic HRPC patients treated with the 10 mg oral dose of atrasentan had a trend toward prolongation in median time to disease progression (defined as new bone or soft tissue lesions, new disease-related pain requiring opioids, new disease-related symptoms that required intervention such as chemotherapy, radiation, or surgery, death) compared with placebo (183 days vs 137 days, $P = 0.13$). In addition, a statistically significant delay in median time to PSA progression was demonstrated (155 days for atrasentan 10 mg vs 71 days for placebo, $P = 0.002$) [23]. In the phase III trial [24], 809 men with metastatic prostate cancer were randomized to atrasentan 10 mg or placebo. The trial was stopped after a median follow-up time of 145 days because based on intent-to-treat analysis there was no significant difference in time to progression in the two arms. Although time to progression was not found to be statistically different from placebo in the intent-to-treat analysis, secondary endpoints demonstrated clinical activity. These included improvement in quality of life, pain scores, and reductions in the rise of laboratory markers, including alkaline phosphatase (a marker of osteoblastic activity) and PSA. In addition, a meta-analysis of pooled phase II and III data [25] demonstrated a significant increase in time to progression ($P = 0.013$), as well as a prolongation in the pain-free duration by 100 days for patients taking atrasentan. In all trials, atrasentan was well-tolerated with mild adverse events such as headache, rhinitis, flushing, and peripheral edema. This data suggests the endothelin axis as a potential target in advanced prostate cancer. Because of failure to demonstrate a perceived clinically relevant benefit, atrasentan has not yet obtained FDA approval, though a large phase III trial of atrasentan in asymptomatic men with a rising PSA after local therapy is ongoing.

Platelet-derived growth factor receptor inhibitors

Imatinib (Gleevec; Novartis Pharmaceuticals Corp., East Hanover, NJ) is a drug that inhibits the tyrosine kinase activity of the platelet-derived growth factor receptor among others. Platelet-derived growth factor receptor is abundantly found in metastatic prostate cancer. It has therefore been evaluated in the treatment of patients with HRPC. A phase II trial in men with biochemical relapse of prostate cancer after definitive local therapy was conducted [26]. Unfortunately, a lack of effect on PSA doubling time and pronounced toxicity at the dose given in the trial (400 mg orally twice daily) led to early closure of this trial. The role of imatinib in combination therapy, however, may be promising, and phase II clinical trials combining imatinib and docetaxel are under way in the metastatic and neoadjuvant settings [27].

Nucleotide-based targeted therapy

Improved understanding of the molecular mechanisms that mediate cancer progression and therapeutic resistance has identified many therapeutic gene targets. Antisense oligonucleotides (ASOs) offer one approach to target genes involved in cancer progression, especially those that are not amenable to small molecule or antibody inhibition [28•]. ASOs are single-stranded, chemically modified DNA-like molecules that are 17 to 22 nucleotides in length and designed to be complementary to a selected gene's mRNA and thereby specifically inhibit expression of that gene (Fig. 1). It is estimated that any sequence of at least 13 bases in RNA and 17 bases in DNA is represented only once within the human genome. Thus, the specificity implicit in the design of ASOs theoretically leads to decreased toxicity. Recently, better chemical modifications of ASOs have increased resistance to nuclease digestion, prolonged tissue half-lives, and improved scheduling. Recent clinical trials confirm the ability of this class of drugs to significantly suppress target gene expression. A number of antisense molecules targeting HRPC are in the preclinical and clinical stages of development (Table 1).

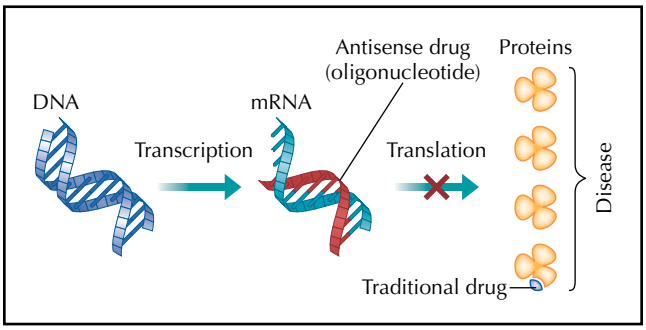

Figure 1. Antisense oligonucleotides targeting progression-associated genes.

Clusterin

The clusterin gene encodes a cytoprotective chaperone protein also known as testosterone repressed prostate message 2. Its chaperone function is thought to stabilize conformations of proteins during times of cell stress, thereby inhibiting protein aggregation or precipitation. In prostate cancer, clusterin levels have been correlated with pathologic grade [29]. In addition, though clusterin expression is low or absent in most untreated hormone-naïve tissues, levels increase significantly within weeks after neoadjuvant hormone therapy [30]. Preclinical studies have also indicated that clusterin suppresses apoptotic cell death in response to androgen withdrawal, chemotherapy, and radiation [31–33]. OGX-011 is a 2nd generation antisense inhibitor targeting the exon 2 translation-initiation site of human clusterin mRNA. Its modified backbone is more resistant to nuclease digestion than other antisense compounds, enabling a tissue half-life of greater than 1 week. In preclinical models of prostate cancer, OGX-011 improved the efficacy of androgen withdrawal, chemotherapy, and radiation by inhibiting expression of clusterin and enhancing the apoptotic response [31–34]. OGX-011 was recently reported to potently suppress clusterin expression

Table 1. Antisense molecules targeting hormone-refractory prostate cancer in development

Target	Compound	Investigator	Phase of development
Bcl-2	G3139 (oblimersen)	Genta, Inc.*	I–III
Clusterin	OGX-011	OncoGeneX Technologies, Inc.†	II
Ribonucleotide reductase	GTI-2501	Lorus Therapeutics‡	II
Protein kinase C-α	ISIS 3521	Isis Pharmaceuticals, Inc.§	II
Raf-1	ISIS 5132	Isis Pharmaceuticals, Inc.§	II
Hsp27	OGX-427	OncoGeneX Technologies, Inc.†	I
IGFBP-2 and IGFBP-5	OGX-225	OncoGeneX Technologies, Inc.†	Preclinical
Androgen receptor	As750/15	Eder et al. [38]	Preclinical

*Berkeley Heights, NJ.
†Vancouver, British Columbia, Canada.
‡Toronto, Ontario, Canada.
§Carlsbad, CA.
IGFBP—insulin-like growth factor-binding protein.

in prostate cancer tissues in combination with ADT [35••]. This trial had a unique design in that patients with localized prostate cancer were administrated OGX-011 before radical prostatectomy, and drug tissue level and serum clusterin expression was determined for each patient and dose level. Concentrations of OGX-011 associated with preclinical effect were measured in tumor tissue, and 90% suppression in clusterin was achieved at 640 mg dose level. A second phase I trial combined increasing doses of OGX-011 with docetaxel in patients with metastatic breast, non–small-cell lung, and HRPCs established a phase II dose for OGX-011 of 640 mg in combination with weekly or every 3 week docetaxel [36]. Four phase II trials of OGX-011 in combination with chemotherapy are now underway in patients with prostate, breast, and lung cancers.

Hsp27

Hsp27 is one of the most strongly induced chaperones during cellular stress, preventing the aggregation and precipitation of damaged proteins. Hsp27 is abundantly expressed in malignant cells and participates in conferring chemoresistance [37]. Accumulating evidence links rising Hsp27 levels with HRPC and development of therapeutic resistance and therefore identifies Hsp27 as a potential therapeutic target. Plans for phase I/II clinical trials using a 2nd generation antisense called OGX-427 targeting the translation-initiation site of human Hsp27 mRNA are planned.

Conclusions

Chemotherapy for HRPC can provide palliation and a modest improvement in overall survival. Skeletal morbidity can be reduced by the use of zoledronic acid and by judicious use of radiotherapy. Further development of novel therapeutics, some of which were discussed in this review, are essential to provide clinicians multiple avenues through which prostate cancer can be effectively treated.

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