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REVIEW ARTICLE

# Current perspectives in the treatment of advanced prostate cancer

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**Abstract** Prostate cancer (PC) continues to be an important world health problem for men. Patients with locally confined PC are treated with either radiotherapy or surgery. However, treatment of more advanced stages of the disease is problematic. Initially, androgen deprivation offers a period of clinical stability, which is however invariably followed by progression to non-responsiveness to hormonal manipulation. Current management of patients with androgen-independent prostate cancer (AIPC) displays modest response rates and achieves only short-term benefit. Recently, knowledge in the complex pathophysiology of advanced PC has led to the identification of mechanisms and target molecules permitting the introduction of new therapies. Consequently, many investigational treatments are ongoing for AIPC in Phase-II and Phase-III trials aiming at the combination of chemotherapeutic regimens along with immunotherapy targeting PC-associated antigens. Other attractive options are gene therapy, as well as the targeting of survival signaling, differentiation, and apoptosis of the malignant PC cells. Further treatment modalities are directed against the tumor microenvironment, bone metastasis, or both. Collectively, the aforementioned efforts introduce a new era in the management of advanced PC. Novel pharmaceutical compounds and innovative approaches, integrated into the concept of individualized therapy will hopefully, during the next decade, improve the outcome and survival for hundreds of thousands of men worldwide.

**Keywords** Prostate cancer · Advanced-stages · Molecular therapy

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## Introduction

Prostate cancer (PC) continues to be an important world health problem for men. Although early stages can be controlled with conventional treatment, advanced PC is a complex biologic entity in which current management achieves only short-term benefit. Recently, knowledge in hormone-refractory PC pathophysiology increased. This enabled scientists to gain insights in the biology of progressive, androgen-independent disease and to focus on the identification of mechanisms and target molecules in order to introduce novel therapies.

Specific therapeutic objectives in advanced PC are different for patients who only have a rising level of serum prostate-specific antigen (PSA) as the sole manifestation of the disease after local therapy, compared to patients who already have detectable metastases. The standard initial systemic therapy for locally advanced or metastatic disease is hormonal management by androgen deprivation therapy (ADT). Yet, the androgen-dependent period in metastatic disease lasts a median time of 14–20 months, and then progresses to a phase when ADT alone fails to control the malignancy despite castrate testosterone levels. This condition is termed androgen-independent prostate cancer (AIPC). Some patients with AIPC respond temporarily to secondary hormonal manipulations. Subsequently, the malignancy no longer responds to further hormonal therapy

and is referred to as hormone-refractory PC or castration-resistant PC. AIPC is a highly resistant state where chemotherapy has yielded poor response rates. New treatment strategies, based on targeted molecular therapy, are now necessary for AIPC management. Indeed, the number of novel agents has increased abundantly in recent years, and combination therapy in Phase-III trials is accelerating, with attention drawn to prognostic factors, survival, and quality-of-life endpoints.

Several variables in PC patients such as life expectancy, disease characteristics, predicted outcomes, and patient preferences must be considered by both patient and physician in individually tailoring the therapeutic scheme. This review focuses on the natural history of PC and its current management principles, with a particular interest in new strategies introduced in clinical trials of AIPC.

## Epidemiology and natural history of the disease

PC is the most common solid tumor amongst men in Western/Northern Europe and in Northern America. In 2003, 9035 new cases were diagnosed in Sweden, and 2,352 men died during the year 2002 [1]. In year 2006 there will be approximately 235,000 men diagnosed with PC and more than 27,000 men will die from this disease in the USA [2]. Globally, the highest rates occur in North America, Australia/New Zealand, and Western/Northern Europe, and the lowest ones in China, South/Central Asia, and Melanesia [3]. Annual incidence rates were markedly higher in more developed compared to less-developed regions, ranging from as low as approximately 1 case per 100,000 males per year in some Asian countries, to 168.9–180.1 per 100,000 person/years in males living in the USA or Sweden respectively [4]. Differences in worldwide PC incidence rates may in part be due to variations in diet (rich in intake of vegetables and low in meat and animal fat reduce PC risk), but are also likely to be influenced by the more vigorous screening with serum PSA testing in developed countries.

In most countries the clinical spectrum of PC is narrowing, as more and more patients are being diagnosed and treated at an earlier stage. With the introduction of PSA testing in 1986 there was a huge surge in incidence, especially of localized and regional stage disease, so that recorded rates doubled between 1986 and 1992. Since then incidence rates have declined, although they remain substantially higher than in 1986, especially in countries like the USA where PC screening is common. Age-specific incidence rates also rose steadily with advancing age worldwide, at 11 per 100,000 among men aged 45–49 years and as high as 14,000 per 100,000 in men aged 75–79 years [5]. As a consequence, three-quarters of all cases are in men aged 65 years or more.

Although the incidence of PC has been increasing, the age-adjusted death rates from PC have begun to decline, in particular in developed countries with a high risk of PC, where survival is significantly better, much of this likely due to cancer being detected at earlier stages by routine screening procedures. In the USA, the majority of newly diagnosed PC cases represent clinically localized disease, but 5–10% of patients have metastatic disease at the time of diagnosis [2]. Thus, mortality rates were only 2.5 times higher in more developed compared to less developed parts of the world, and this reflects to a mortality-to-incidence ratio of only 0.13 in North America, compared to 0.80 in Middle/Western Africa [3, 5]. As a result, the lifetime risk of developing PC in men living in the USA has risen to 17.9%, whereas the risk of dying of the disease is only 2.6–4.3%.

The natural history of PC is not as well defined. It has been estimated that one in every three men over the age of 45 will demonstrate histological evidence of PC during their lifetime. This frequency increases with age; histological evidence of PC may be present in up to 80% of men by age 80. Despite its protracted course in some patients, it is clear that the disease pursues a more aggressive course in others. Gronberg and colleagues demonstrated that the likelihood of dying of PC increases with decreasing age at diagnosis [6]. Indeed, patients less than 60 years of age had a greater than 80% risk of dying; meanwhile patients over 80 years of age had less than 50% risk.

PC has a quite predictable pattern of progression. As an organ-confined tumor it increases in volume. Subsequently, it invades into and through the periprostatic fat into the wall of the seminal vesicle. Clinically detectable lymphatic metastases or bone metastases become apparent years later or may present concurrently with the diagnosis of locally advanced disease [7, 8]. The skeleton is the most common site of metastasis, particularly the axial skeleton by means of osteoblastic metastases.

## Carcinogenesis, progression and metastasis

Greater than 95% of human PC are adenocarcinomas arising from the epithelial cells that line the glands and ducts of the prostate [8]. PC develops through the accumulation of genetic alterations that result in an increase in cell proliferation, decrease in cell death, arrest of differentiation, and furthermore confer the ability to invade, metastasize, and proliferate in a distant site. It is generally characterized by low mitotic rates, tumor heterogeneity, and significant stromal elements.

Phenotypic alterations during prostate carcinogenesis include a reduction in defense against carcinogen-induced damage, inflammation, changes in androgen signaling and

in growth regulatory genes. Prostatic inflammation over years, perhaps decades, is thought to modulate carcinogenesis [9]. Histological changes are present in the prostates of men in their 20s, yet the diagnosis is typically made 3–4 decades later, which suggests that the development of the disease is a long multistep process. Initially there is proliferation within ducts, termed prostatic intraepithelial neoplasia (PIN), adjacent to areas of proliferative inflammatory atrophy (PIA), followed by loss of the basal cell layer in prostatic glands, the development of an anaplastic morphology with nuclear pleomorphism and prominent nucleoli, invasion of the basement membrane, overt invasion, and finally metastatic spread. PIA and PIN are often associated with chronic inflammation. PIN is further defined by the presence of cytologically atypical or dysplastic epithelial cells within architecturally benign-appearing glands and acini and is subdivided into low and high grade. Only high-grade PIN is considered a precursor for invasive carcinomas [10].

The molecular pathogenesis of PC displays a great deal of heterogeneity both between individuals as well as within an affected organ. The diversity of currently identified somatic genetic abnormalities associated with PC suggests that there is not a single-dominant molecular pathway required for prostate carcinogenesis. Somatic alterations can accumulate over several decades before PC appears [11]. Losses at 8p, 13q and gains at 16q and 17q are significant early events, followed by 6q loss and 8q gain. Significantly late genomic changes included gains at 7p and 7q [12]. However, more than 70% of the pT1–T2 tumors did not display chromosome-level imbalances; this finding could indicate that sub-microscopic genetic or epigenetic changes are responsible for these morphologically confirmed cancers. The frequent finding of DNA losses suggests inactivation of tumor suppressor genes, and this occurs mainly through allelic deletion, point mutations, gene silencing by promoter methylation, and a decreased level of the message or of the protein product by proteasomal degradation [13]. One of the earliest changes identified is a loss of expression of the glutathione S-transferase pi-1 (GSTP1) gene. GSTP1 protects against oxidative stress at sites of inflammation or genome damage. Genes potentially involved in prostate carcinogenesis are also: (i) tumor suppressor genes as N33, MXI1, P53, RB1, DCC; (ii) oncogenes as MYC, ERBB2, RAS; (iii) metastatic genes as CDH1 (E-cadherin), CTNNA1 (α-catenin), CCAM, KAI1, CD44, PTEN; (iv) androgen cascade related genes such as androgen receptor (AR), HSD3B2 (3$\beta$-hydroxysteroid dehydrogenase), and SRD5A2 (5α-reductase) [14].

Recently, proteomics technology was used to analyze the protein expression profile of PC, which was shown to differ from that of benign tissue. Among proteins overexpressed in PC were transcription factors, enzymes involved in gene silencing, protein synthesis, degradation, and energy metabolism, heat-shock proteins, structural proteins and membrane proteins [15]. Also, proteins like epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF), together with their corresponding receptors, have been reported to be overexpressed in PC. Insulin-like growth factor-1 and -2 (IGF1, IGF2) and transforming growth factor-α and-$\beta$ (TGF-α, TGF-$\beta$) and their receptors, have also been implicated. Moreover, increased expression of telomerase has been detected in 85% of PCs.

The current view is that PC is composed of cells with three distinct cellular phenotypes: androgen-dependent, androgen-sensitive, and androgen-independent [16]. Knowledge of androgen physiology is important in PC as the prostate gland requires both androgens and polypeptide growth factors for proliferation, differentiation, and maintenance of function [17, 18]. The testis is the site where 90–95% of androgens are synthesized, the remainder being mainly of adrenal source. On entrance into the cell, testosterone is converted into a number of metabolites that mediate the intracellular processes under androgenic control. The most active of these metabolites, dihydrotestosterone (DHT), is produced by the action of 5α-reductase. Once in the cytoplasm, DHT binds with high affinity to the AR. The hormone-receptor complex is then translocated to the nucleus, where it influences the transcriptional activity of androgen-responsive genes involved in cell growth. In the prostate, androgens (predominantly) and growth factors (ECF, TGF-α, KGF, bFGF, and IGF1) function primarily as growth and survival mediators. However during prostate tumorigenesis this system is deregulated, allowing for growth-stimulatory interactions to occur between androgens and growth factors [18]. Stimulation of PC cells with growth factors can decrease the requirement for androgen, and the expression of these growth factors and receptors increase as PC progresses [19]. In late-stage AIPC there is an increase in the production of growth factors, which retains AR signaling through their cognate receptors, despite the near absence of circulating androgens [18].

During androgen-independent progression, PC cells develop a variety of cellular pathways to survive and flourish in the androgen-depleted environment. Two main pathways have been identified: the hypersensitive pathway and promiscuous one [20]. In the former, more AR are produced and are activated despite reduced levels of DHT. This increased production of AR is likely the result of PC cells developing more copies of the AR gene (gene amplification) as a result of mutation, or through selective pressure of the androgen-depleted environment causing the cells with fewer AR to die off and the clonal expansion of cells with more AR. The specificity of the AR can also be broadened by mutations, creating a promiscuous receptor

that can be activated by non-androgenic steroid molecules. The central role of AR in the growth of PC makes it an attractive target for novel therapeutic strategies that inhibit its activity. Possible points of blocking the AR are the intracellular signaling proteins, the interaction between the AR and co-activators required for its function, as well as the DNA binding of AR [21, 22]. Eventually, cell survival occurs independent of AR activation, the best example being upregulation of the molecule BCL-2 by AIPC cells, which protects them from apoptosis when deprived of testosterone. Other mechanisms involved include the activity of cells that support the growth of PC, such as neuroendrocrine cells that secrete neuropeptides [23, 24].

Bone is the most frequent site of PC metastasis. The establishment of a metastatic focus in bone involves multiple steps, including adhesion of the tumor cells to endothelial cells in the marrow and migration through fenestration in the endothelial cell layer. Loss of genes that affect normal cell adhesion promotes detachment of malignant cells and can also serve to activate genes that promote invasion through the basement membrane into the blood vessel, a process necessary for metastatic spread. In this direction E-cadherin, a Ca-dependent cell surface glycoprotein that functions as an epithelial cell-cell adhesion molecule, is decreased in metastatic progression [25].

## Diagnosis, staging, monitoring, and prognosis

Initial detection nowadays for the majority of tumors is based on an abnormal PSA level and less commonly on an abnormal digital rectal examination. PSA is a 28-kD protein of the kallikrein family, a group of serine proteases whose genes are found in chromosome19q13. It is synthesized in the ductal and acinar epithelium and is secreted into the lumen, being organ specific but not cancer specific. Once released from the prostate, it circulates in the serum as free or complexed form. PSA emerged as the most important tumor marker for PC and its widespread use in the clinical setting for PC screening has resulted in a dramatic shift in the proportion of neoplasms that are organ confined at initial detection. PSA by itself is an androgen-responsive gene, and reducing androgen levels or blocking androgen binding to the AR results in lower PSA values.

Confirmation of diagnosis requires a biopsy of the prostate gland, usually performed by a needle under transrectal ultrasound guidance. A pathologist then assigns a Gleason primary and secondary grade to the biopsy specimen. Clinical staging is based on the TNM 2002 classification from the American Joint Committee on Cancer [26]. Patients are stratified for initial treatment recommendations based on anticipated life expectancy and whether they are symptomatic or not. Pre-treatment clinical features that correlate with prognosis are TNM stage, Gleason score and serum PSA level [27]. Pathologic criteria that are independent factors include tumor grade, surgical margin status, the presence of extracapsular disease, seminal vesicle invasion, or involvement of pelvic lymph nodes. Clinical stage at presentation has an important impact on survival and the ultimate risk of death from PC. The 15-year corrected survival was 80–90% for patients with clinical stage I disease, 35–70% for patients with clinical stage II-III disease and 10–20% for patients with metastases at diagnosis [8, 28]. Histological tumor grade also appears to be a very important factor predicting disease progression [29]. Only 16% of patients with well-differentiated tumors died of PC, in contrast to 38% of patients with moderately differentiated and 68% of patients with poorly differentiated neoplasms [30]. The Gleason tumor grading system is an important prognostic indicator for the eventual death from PC (i.e. 4–7% of patients with Gleason 2 to 4 disease, 18–30% of patients with Gleason 6 disease, and 60–87% of patients with Gleason 8–10 dying of PC within 15 years of diagnosis). PC is among the slowest growing of all human malignancies and its proliferation rate correlates highly with the Gleason score, with high-grade tumors (Gleason score 8–10) being much faster growing than low-grade ones (Gleason score 6 or less) [31].

The National Comprehensive Cancer Network (NCCN) Guidelines v2.2005 [32] incorporate a risk stratification scheme that uses stage, grade, and PSA to assign patients to risk groups that predict the probability of biochemical failure after definitive local therapy. The Clinical Practice Guidelines of the NCCN panel recommend stratification of recurrent disease risk using the available predictive features in four groups: (i) low risk of recurrence, which includes tumors stage T1–T2a, a low Gleason score (2–6) and a PSA level below 10 ng/ml; (ii) intermediate risk of recurrence, any T2b–T2c cancer, Gleason score of seven, or PSA value of 10–20 ng/ml; (iii) high risk of recurrence, stage T3a, Gleason score of 8–10, or PSA level greater than 20 ng/ml; and (iv) very high risk of recurrence, clinical stage T3b–T4, or non-localized cancer (any T, any N, M1). Patients with multiple adverse factors may be shifted into the next higher risk group.

Since recurrence after definitive treatment for PC is a significant problem, monitoring biomarkers are essential. In the early 1990s, when the PSA assay became widely available, monitoring the response to agents in clinical trials began to be measured and reported in terms of a PSA response. Serum PSA provides a valuable tool for monitoring the response of PC patients after surgical/radiation/antiandrogen therapies. Large studies have shown that total serum PSA correlates with increasing clinical stage, final pathologic stage, and tumor volume. Without PSA

determination, measurable disease is evaluable in only 10–20% or patients. The use of the PSA endpoint, although not validated in a Phase-III trial as a surrogate for response or survival, has become the standard method to screen the activity in Phase-II trials [33, 34]. Detailed guidelines on PSA monitoring were suggested in a Consensus Conference in 1999 [35]. Generally, it is recognized that PSA relapse precedes anatomic relapse typically by 6–48 months [36]. In conjunction with pathologic stage and Gleason grade, post-prostatectomy and post-radiotherapy PSA kinetics may provide a means of predicting the likelihood of a patient having an occult metastasis [37]. Also, rapid PSA-doubling times have been shown to be associated with higher PC-specific mortality [38–40].

Different imaging studies complement clinical and pathologic information in localizing primary treatment failure. These modalities include trans-rectal ultrasound, bone scan, pelvic computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). Distinguishing between local recurrence and distant failure is important in making subsequent treatment decisions. In clinical trials the PC response and progression are amenable to assessment using standard Response Evaluation Criteria in Solid Tumors (RECIST) [41].

## Treatment strategies in early-stage PC

For the management of early-stage tumors, we have learned that ''waiting and watching the wrong tumor'' can allow the window of curability to close and adversely affect both the morbidity and mortality of the disease. A treatment plan should be based on the life expectancy of the patient, the nature of the cancer (stage, grade, PSA), the effectiveness and side effects of a given treatment, the experience of the treating physician, and the patient's own preference. Generally, optimal treatment of PC requires assessment of risk, as predicting prognosis is essential for patient decision-making, treatment selection, and adjuvant therapy. To quantify risk more accurately different nomograms have been devised, the most widely used of them being an algorithm that combines clinical stage, biopsy Gleason grade, and preoperative PSA level [42]. Nomograms allow us to incorporate all established prognostic factors for an individual patient and can help us to take an analytic decision, taking into account the immediate risk of treatment-associated mortality and morbidity with the ongoing risk of a clinically significant event from cancer, including local recurrence or metastatic spread. Such risk stratification schemes are also available for predicting the 5-year freedom from recurrence following treatment [43]. The next generation of nomograms will incorporate pre- and post-treatment variables to predict important clinical endpoints.

Watchful waiting is a valid treatment option whenever the probability that the cancer will progress and produce symptoms within the patient's life is low. Consequently, for patients with a life expectancy of less than 5 years and without clinical symptoms, further workup or treatment may be delayed until symptoms develop. On the other hand, active surveillance is a more closely supervised strategy, which applies to selected younger patients with early localized PC who are initially managed expectantly by means of PSA measurement, digital rectal examination, and repeat biopsies, with the intention to offer curative treatment if progression occurs. This represents a balanced compromise between radical therapy and watchful waiting with palliative therapy when necessary.

The techniques of surgery and radiation, which are the standards for the management of localized disease, continue to be refined so that cure rates are increasing while morbidity declines. This makes long-term outcome data not representative of current therapies. Stage for stage, the survival outcome was similar for surgery and radiation therapy in retrospective analysis of PC series [44]. It has been frequently stated that although the results of radiation and radical surgery are similar up to 10 years, there may be a selective decrement in survival and disease-free survival for irradiated patients at longer follow-up periods [8]. Radical prostatectomy (RP) should be considered in those patients with organ-confined disease, where a clear surgical margin is possible. Because of potential perioperative morbidity, RP should be reserved for patients whose life expectancy is 10 years or more and have no serious comorbid conditions that would contraindicate elective surgery [32]. Pelvic lymphadenectomy is not considered a therapeutic intervention, but patients at intermediate to high risk of lymph node metastases are benefited. Technical refinements in RP have resulted in lower rates of urinary incontinence, higher rates of recovery of erectile function, less blood loss with fewer transfusions, shorter hospital stays, and lower rates of positive surgical margins.

Radiotherapy (RT) for PC shows several distinct advantages over surgical therapy. RT avoids complications (i.e. bleeding) as well as risks associated with anesthesia. This therapy includes a very low risk of urinary incontinence and stricture as well as a good chance of short-term preservation of erectile function. Side effects as cystitis and proctitis may occur during or after RT. Contraindications to RT include prior pelvic irradiation, active inflammatory disease of the rectum, permanent indwelling Foley catheter, and morbid obesity. Both total dose and dose rate may have a role in the treatment of PC. The total dose of radiation therapy with external beam treatments is in the neighborhood of 75 Gy. The total biologically equivalent

dose delivered with brachytherapy is 145 Gy ($^{125}$Iridium) or 100 Gy ($^{103}$Palladium). Three-dimensional conformal radiation therapy (3D-CRT) was developed to overcome the deficiencies of conventional 2D approaches. Three-D treatment planning incorporates anatomic definition of each subvolume within the entire space irradiated (target volume) and precise calculation of the dose delivered at each point. Intensity-modulated radiation therapy (IMRT) is an advanced form of 3D-CRT, its most distinctive feature being the combination of multiple intensity-modulated fields that produce custom-tailored dose distributions around the target volume with steep dose gradients at the transition to normal tissue [45].

For patients undergoing RP, should the margins be positive, follow-up options include RT or observation. RT can reasonably be used after recuperation from surgery; alternatively, close observation is acceptable until a detectable PSA develops (>1.0 ng/ml) [46]. Androgen deprivation has been explored both before and after RP or RT. Neoadjuvant androgen deprivation has the potential to reduce tumor size and improve resectability, as well as to allow for the deliverance of maximal radiation dose levels without exceeding the tolerance of the surrounding normal tissues [47–50]. However, adjuvant antiandrogen therapy is not a standard treatment at this time. RT has also been used as adjuvant postoperative treatment after RP in patients with T3–T4 disease in an attempt to eradicate microscopic residual tumor in the periprostatic tissues or adjacent pelvic lymph nodes. Several studies on this matter indicate that, whereas postoperative pelvic irradiation can control local disease, an impact on survival is less clear [51].

## Conventional treatments and their outcome in late-stage PC

Primary ADT and secondary hormonal therapy remain the cornerstones of treatment for advanced PC. Androgen deprivation therapy, consisting of surgical or medical castration, has been longtime the standard of care for patients with initially disseminated or metastatic cancer. Orchiectomy and the administering of a bolus of an LH-RH analog reduces circulating testosterone by around 95% to levels of <20 ng/ml. ADT significantly reduces morbidity associated with metastatic disease such as spinal cord compression, ureteral obstruction, and bone pain [52]. On the other hand, it is associated with numerous side effects, including hot flashes, decreased libido, mood changes, metabolic changes, osteopenia, and increased risk of bone fracture [53]. Various clinical studies have addressed the question of whether or not to initiate ADT early after serologic progression. Initially, the Medical Research Council (MRC) and Veterans' Administration Cooperative Urologic Research Group (VACURG) studies gave contradictory results, the first showing an overall and disease-specific survival advantage, and the second failing to confirm it [54]. It now seems that early intervention is favorable for patients with high-risk clinical features such as advanced stage primary tumor, high Gleason score, lymph node metastases, and pretherapy PSA > 20 ng/ml. Androgen independent cancers progressing despite combined androgen blockade will sometimes show a PSA response upon withdrawal of the antiandrogen. This can result in PSA decline of more than 50% in approximately 15% of patients, with response duration of 3.5 months [55].

Androgen deprivation initially produces a decline in PSA and regression of measurable tumor mass, a period of clinical quiescence or stability in which the tumor does not change in size. This is followed within a variable period of time by a rise in PSA, proliferation of the tumor and clinically detectable tumor regrowth. Eventually, all patients are expected to progress despite hormonal treatment [7, 8, 56]. Indeed, the major cause of death from PC is a result of progressive androgen-independent disease. Tumors that progress despite castrate levels of testosterone have been variably classified as hormone-resistant, hormone refractory, androgen-insensitive, or androgen-refractory. Failure of first-line androgen ablation can be manifest in several ways. In some patients, it is just a rising PSA, in others coupled to progression of osseous disease, and in some there is visceral spread with or without osseous disease. Responses to the first-line systemic treatment of ADT last on average 14–20 months [57]. The development of AIPC is often an ominous clinical finding since median survival remains approximately 15 months in most studies, although in some trials it has been reported to extend to 4 years [58]. A low proportion of patients with progressive disease and castrate levels of testosterone respond to second and third-line hormonal manipulations.

After ADT failure AIPC patients are still susceptible to secondary hormonal treatments with second-line antiandrogens, or adrenal androgen inhibitors [56]. These agents are able to induce PSA and radiographic responses and may provide symptomatic improvement. Non-steroidal antiandrogens such as bicalutamide, flutamide, and nilutamide reduce the stimulatory effects of circulating androgens by directly blocking AR. High-dose bicalutamide (150–200 mg daily) induced PSA responses of more than 50% in 20–25% of patients [59]. Similar results were obtained using 375 mg of flutamide daily [60]. AIPC treated with nilutamide showed PSA responses of more than 50% in 40% of patients, with a median time to progression of 4.4 months. Phase-II studies reported a lower response rate for nilutamide and flutamide in AIPC patients who had been previously treated with bicalutamide. Inhibitors of adrenal androgen production such as

ketoconazole, costicosteroids, and aminoglutethimide act to further reduce circulating androgens by eliminating the 10% of androgens that are normally secreted by the adrenal glands. Ketoconazole, the most commonly used one, and hydrocortisone showed PSA response of more than 50%, with median response duration of 30 weeks [61]. Estrogen therapies as diethylstilbesterol (DES), transdermal estradiol, and conjugated estrogens are thought to have a multifactorial mechanism of action in the treatment of AIPC. Of the estrogens, DES is the best characterized, showing occasionally PSA responses of more than 50% in 21–86% of patients, although its use has been associated with serious side effects, such as deep venous thrombosis and cardiovascular death [62].

Systemic chemotherapy should be reserved for AIPC patients, where it can confer a survival benefit [63]. Although PC appears to be particularly sensitive to agents that target the cytoskeleton such vinblastine, vinorelbine, etoposide, paclitaxel, and docetaxel in combination with estramustine, only docetaxel showed an overall survival benefit of approximately 2.5 months [64, 65]. Docetaxel, a semisynthetic taxane, is likely to have multiple mechanisms of antineoplastic activity, but microtubule stabilization is the most widely accepted one. Based on these data the FDA approved the regimen of docetaxel 75 mg/m$^2$ every 3 weeks in combination with prednisone 5 mg orally twice per day for the treatment of symptomatic advanced PC. Mitoxantrone with prednisone has been shown to provide palliative benefit in patients with painful bony metastases from AIPC. In a Phase-III trial conducted by Kantoff and colleagues of the Cancer and Leukemia Group B, it was shown that approximately one-third of patients receiving mitoxantrone chemotherapy demonstrated significant pain relief for an average of 8 months [66].

RT provides effective palliation for patients with advanced PC. For patients with a single site of osseous pain or with limited obstructing masses or lymph nodes, external beam radiation has been demonstrated to be very effective in controlling progressive disease. For patients with multiple sites of bone involvement and pain, systemic radioisotopes administered intravenously may have significant therapeutic effects. The two most commonly used radioisotopes are $^{89}$Strontium and $^{153}$Samarium. The combination of radioisotopes with chemotherapy may lead to increased effectiveness for the palliation of painful bone metastases in patients with AIPC [67].

Valuable and easy practice guidelines for AIPC were recently suggested by Pienta and Smith [63]. Initially, patients are stratified into three broad categories: biochemical-only disease, asymptomatic disease with positive scans, and symptomatic disease. Briefly, if AIPC patients have biochemical-only disease, a decision must be made as to whether to treat or to follow expectantly. This first decision can be based, at least partially, on the speed at which the PSA is doubling (PSAdt) as well as other factors such as age and overall health status. Patients with slow doubling times (>8–12 months) are suitable for monitoring. Bone scans can be performed every six months or on a yearly basis. Patients with rapid PSAdt (<6–8 months) should be considered for clinical trials. Asymptomatic patients with a rising PSA and a positive bone scan should also be considered for clinical trials and are eligible to receive docetaxel. Patients with visceral disease with or without bone disease are more likely to be started on cytotoxic chemotherapy while still asymptomatic than are those with bone-only disease. Docetaxel is considered to be the first line agent of choice here. However, mitoxantrone has a proven palliative benefit in patients with symptoms and can be considered as a first-line agent in patients who may not tolerate docetaxel. Because neither of these agents is curative, clinical trials for these patients should always be considered. Symptomatic patients with sites of pain secondary to bone lesions should be considered for palliative RT. Zolendronic acid, a bisphosphonate, has shown considerable efficacy regarding the prevention or delay of skeletal events such as vertebral and non-vertebral fractures, spinal cord compression and the need of radiation or surgery to the bone [68]. It has been proposed as a standard treatment in patients with bone metastasis, although prognostic factors that might predict the risk of skeletal-related events were not considered. Patients with metastases to the spine with or without spinal cord compression can be treated with external beam radiation. Alternatively, patients with spinal cord compression can be treated with surgery or a combination of surgery/radiation.

The assessment of quality-of-life measures is also critical, particularly since none of the systemic treatments is curative. A critical aspect of the management is palliation of symptoms. Supportive measures can include a transurethral resection of the prostate (TURP) to relieve outlet obstruction, the placement of stents or nephrostomy tubes to improve renal function, steroids to relieve cachexia and to palliate the pain associated with osseous disease, and erythropoietin to correct the anemia related to androgen deprivation.

The conventional treatments of AIPC patients in use achieve partial results. Survival of AIPC patients is in the order of 12–46 months, depending on whether they display only a PSA rise or overt radiographic progression [69]. Patients that are asymptomatic or have slow PSA doubling times may have a survival of over 2 years. Effective chemotherapy treatments based on docetaxel provides just a 2–3-month survival benefit [64, 65]. Therefore, newer and more effective treatments are urgently needed for the treatment of AIPC.

## New targets, new strategies, new clinical trials

There is no debate that therapies beyond hormones are needed to improve outcomes for patients with advanced PC. A number of novel agents has been introduced in clinical trials for AIPC treatment, including molecular signal transduction inhibitors, stem-cell targeted therapy, anti-angiogenic compounds, vaccines and immunomodulating agents, differentiation agents, cytotoxics, and pro-apoptotic agents [70–72]. Knowledge of the molecular determinants of progression, relapse after local therapy, chemotherapeutic resistance, and hormone refractoriness remains essential in the rational design of clinical trials of these agents [18, 73, 74].

### Clinical trials with new cytotoxics

The dose limitations of docetaxel therapy in metastatic AIPC are predominantly those of peripheral neurotoxicity and myelotoxicity. One agent developed for second-line therapy is satraplatin, a novel oral platinum compound that is well tolerated and shown to improve survival over corticosteroids in the ongoing SPARC phase-III trial [75]. The epothilones are a class of microtubule-targeting cytotoxic agents in development for second-line and relapsed hormone-refractory PC. Initial results demonstrated comparable PSA declines and progression-free survival to that seen with docetaxel-based therapy [76].

### Gene therapy

Numerous gene therapy strategies are being tested in PC [72]. The main objectives include the direct killing of malignant cells by replication-competent oncolytic viruses and the indirect killing through the delivery of suicide genes. Other major aims of gene therapy involve the insertion into tumor cells of a gene encoding a tumor suppressor, pro-apoptotic, or immune-activating factor, as described below. Suicide gene therapy, also known as gene-dependent enzyme prodrug therapy, requires introduction of a gene encoding a drug-metabolizing enzyme into the target cells, followed by systemic administration of a non-toxic prodrug. Two of the most commonly used enzyme-prodrug combinations in gene therapy protocols are HSV gene for thymidine kinase (TK, used with ganciclovir), and the cytosine deaminase (CD, used with 5-fluorocytosine).

The ideal method of delivery would transfer the genetic material efficiently and specifically to the targeted organ. Through the use of prostate-specific promoters and enhancers, the expression of a therapeutic gene can be limited to cells that contain the appropriate activators and transcription factors. Prostate-specific membrane antigen (PSMA) enhancer was discovered within the third intron of the gene [77], and has been used for prostate-specific gene delivery under low androgen levels [78]. The safety and efficacy of gene therapy for PC has been demonstrated through various preclinical and clinical trials, and potentially holds the greatest promise. Currently, 56 gene transfer protocols in treating advanced PC are ongoing in clinical trials [71].

### Clinical immunotherapy trials

Immunotherapeutic approaches to AIPC are based on the premise that the immune system, if properly mobilized, can eradicate malignant cells. Immunization strategies range from whole-cell vaccines to T cell-based vaccination against defined PC proteins. Among the most frequent tumor-associated antigens (TAA) targeted are PSA, PSMA, prostate acid phosphatase (PAP), prostate secretory protein-94 (PSP94), and the mucins MUC-1 and MUC-2. A key issue in developing an immune response is breaking tolerance. Several vaccination strategies have progressed beyond phase-II testing in PC, including Provenge (a PAP-activated dendritic cell-based vaccine), and GVAX, a whole-cell allogeneic vaccine. Both of these agents are under evaluation in the phase-III setting.

Provenge (APC-8015) is an investigational therapeutic vaccine that uses autologous dendritic cells collected from patients through leukaphereses as antigen presenting cells (APCs) [79]. Cells are loaded with a recombinant fusion protein of PAP linked to GM-CSF and reinjected intravenously every 2 weeks. Early trial results have demonstrated activity and possible increased survival in patients with AIPC [80]. A randomized Phase-III trial studying the effectiveness of APC-8015 demonstrated a significant survival advantage of vaccinated patients (25.9 months vs. 21.4 months for placebo), although the time to disease progression was not significantly improved [81]. GVAX on the other hand is a form of active immunotherapy using whole-cell allogeneic prostate cell lines (PC3 and LNCaP) virally transduced to express GM-CSF as an immune adjuvant, lethally irradiated, and injected intradermally [82]. Data from Phase-I/II trials testing the efficacy of such an approach demonstrated that it is safe and immunologically active. Phase-III studies examining GVAX in combination with docetaxel and prednisone or along with induced lymphopenia and haematopoietic reconstitution have been initiated [83]. Another vaccine, Onyvax-P, is made from a combination of three irradiated allogeneic cell lines that express antigens representative of different stages of PC (primary, lymph node metastasis and bone metastasis). Data from a Phase-II trial suggest that Onyvax-P vaccination results in an increased progression-free survival in AIPC patients [84].

Recombinant attenuated poxviruses (vaccinia, fowlpox, and canarypox) have been used for viral gene delivery into dendritic cells. The transduction of these viruses in mammalian cells is safe, without the risk of insertional mutagenesis as they do not integrate into the cell-genome. The Eastern Cooperative Oncology Group conducted a Phase-II clinical trial to evaluate the prime/boost vaccine strategy using vaccinia virus and fowlpox virus expressing PSA in patients with biochemical progression after local therapy for PC. Of the eligible patients, 45.3% remained free of PSA progression at 19.1 months and 78.1% demonstrated clinical progression-free survival after 2 years of follow-up [85]. TRICOM is a modification of these poxvectors to boost their effectiveness in eliciting an immune response by including the insertion of three genes encoding molecules important for providing the second signal for T-cell activation through different but collaborative pathways. A Phase-III randomized study of vaccinia-PSA-TRICOM vaccine, fowlpox-PSA-TRICOM vaccine, and sargramostim (GM-CSF) versus empty vector control in patients with metastatic AIPC is now testing this strategy [83].

Vaccination strategies using plasmid DNA compared to the use of a viral gene delivery system have particular advantages: administration of plasmid DNA does not result in the expression of irrelevant proteins and thus immune reactions to neutralize the immunizing vector are not generated, as is the case for recombinant virus, this way enabling repetitive immunizations [86]. A Phase-I trial of DNA vaccination with a plasmid expressing PSA in patients with AIPC demonstrated that this practice is safe and can induce cellular and humoral immune responses against PSA [87]. An analogous Phase-I study of a PAP DNA vaccine has also been conducted [88]. These results are encouraging and the corresponding Phase-II trials are awaited.

Antibody-based therapies for several cancer types have now been approved by the FDA. Radiolabeled antibodies against PSMA have been under development for several years. As a target, PSMA seems ideal: it is a cell-surface glycoprotein specifically expressed in PC and its levels increase with grade and androgen ablation. Murine J591 antibody recognizes the extracellular domain of PSMA, and has been studied for efficacy and toxicity conjugated to multiple different radiopharmaceuticals, including $^{90}$Ytrium, $^{131}$Iodine and $^{177}$Lutetium. This should allow specific therapeutic targeting of PSMA-expressing cells [89]. MLN591 is humanized form of the former that has been employed as a naked molecule, radioconjugate, or chemoconjugate. Phase-I clinical trials, alone or in combination with anti-CTLA-4/MDX-010 are ongoing.

## Therapies targeting cellular survival signalling

Targeted therapy generally refers to inhibiting specific signal transduction pathways important in cancer cell growth or the function of cells that support tumor expansion, such as endothelial cells. Targeted therapies include blocking the interactions of ligands with their receptors, the activation of the receptor, or the downstream signal-transduction pathways within the cell [90, 91].

Twenty seven percent of the 364 cancer-causing genes registered actually encode for protein kinase domains [92]. Given the high proportion of kinases involved in cancer and the clinical and commercial success emerging from various kinase-directed drugs, this class of gene products has become the most frequently targeted in cancer drug discovery. The prototypical target kinase is vascular endothelial growth factor (VEGF) receptor. PC is known to overexpress VEGF and its receptors and plasma VEGF levels have been reported as a significant independent predictor of survival in AIPC [93]. Bevacizumab is a monoclonal antibody that binds to VEGF and inhibits angiogenesis. A Phase-III trial by the Cancer and Leukemia Group B (CALGB) comparing docetaxel plus prednisone with docetaxel/prednisone/bevacizumab is ongoing [83]. The activation of VEGF receptors can also be hindered with the small molecular tyrosine kinase inhibitor aminophthalazine (PTK787), which blocks the function of all known VEGF receptors [94]. Sorafenib (BAY 43-9006) and Sunitinib (SU011248) are potent oral inhibitors that block several tyrosine kinase receptors, among others VEGF-R and PDGF-R, involved in neovascularization and tumor progression [95, 96].

Several other agents that utilize the paradigm outlined above are in clinical trials for AIPC [97]. These include inhibitors of platelet-derived growth factor receptor (PDGF-R), epidermal growth factor receptor (EGF-R), and insulin-like growth factor (IGF) [98]. Additional agents with anti-angiogenic properties include thalidomide and its analog. All of them are now in Phase-II trials. Their high potency in terms of anti-angiogenic properties and oral availability make them attractive as therapeutic agents. The growth of new blood vessels can also be blocked by inhibiting integrin function. EMD 121974 (Cilengitide) is the inner salt of cyclized pentapeptide that is a potent and selective integrin antagonist [99], and NCI trial 6735 is evaluating it.

Other intracellular signaling pathways including the BCL-2 family, the MAP kinase pathways, the RAF proteins, and mammalian target of rapamycin (mTOR) have been targeted in AIPC [100]. mTOR, which lies downstream of PTEN and AKT, plays a critical role in cell growth and survival. PTEN is commonly lost in advanced

PC. AKT on the other hand has been linked to progression and biochemical recurrence [101]. Several inhibitors of mTOR, including rapamycin and its derivatives CCI-779 and RAD001, are being tested in clinical trials.

## Therapies targeting cellular differentiation and the apoptotic pathway

Calcitriol, the active form of the steroid hormone vitamin D, has a spectrum of effects on epithelial cancer cells, including induction of differentiation, cell cycle arrest, and apoptosis. Additionally, its receptor is present in many benign and malignant epithelial cells, including PC, where in vitro results suggest that it has growth inhibitory, proapoptotic, and differentiating properties. Calcitriol inhibits the growth of several types of cancer in vitro and has demonstrated activity as a single agent in patients with AIPC [102]. Based on favorable Phase-II results of calcitriol and docetaxel in combination [103], a study with typical Phase-III survival endpoints is underway.

Other differentiation strategies include the use of inhibitors of histone deacetylase and DNA methyltransferase, enzymes responsible for the epigenetic silencing of gene expression, including those implicated in the regulation of cell survival, proliferation, differentiation, and apoptosis. Aberrant hypermethylation and gene silencing of specific promoter regions in PC has been described, such as of the antioxidant enzyme GSTP1 and the tumor suppressor p21 [104]. Phase-II studies are planned using orally bioavailable histone deacetylase inhibitors in metastatic AIPC [105].

Two pro-apoptotic strategies have progressed to the Phase-II setting, the antisense oligonucleotide directed to the BCL-2 mRNA (oblimersen sodium, G3139) and the proteasome inhibitor bortezomib. In PC, BCL-2 family proteins (BCL-2 itself and $BCL_{XL}$), and c-myc have been identified as possible targets for this antisense approach, where the introduction of a specific complementary or antisense strand of single-stranded nucleic acid can bind to the abundantly transcribed RNA strands, leading to their degradation before translation occurs. A Phase-II study of oblimersen sodium with docetaxel in AIPC demonstrated an encouraging response rate and overall median survival [106].

NF-$\kappa$B family transcription factors are potent inhibitors of apoptotic cell death. Specific inhibitors of NF-$\kappa$B family proteins have yet to progress to the clinic, but preclinical studies indicate that agents that specifically inhibit the proteasome also reduce levels of NF-$\kappa$B. Bortezomib, a novel peptide that inhibits 26S proteasome activity, tested in a Phase-I/II trial combined with docetaxel in patients with advanced AIPC gave evidence of a clinical benefit [107]. A Phase-II study of bortezomib with or without ADT in patients with early relapsed PC (PSA only without metastasis) is ongoing.

## Other strategies for AIPC treatment

The propensity of PC cells to metastasize to bone is leading to the design of novel therapies targeting both the cancer cell as well as the bone microenvironment. The production of an osteoblastic metastasis is the result of a complex interaction between prostate tumor cells, osteoclasts and osteoblasts [73]. Different factors stimulate osteoblast proliferation, a major one being endothelin-1 (ET-1). ET-1, a potent vasoconstrictor, has been demonstrated to be an important mediator of PC cell-osteoblast interactions as it inhibits osteoclast activity, pushing the osteoblast-osteoclast balance in favor of new bone formation [108]. Increased expression of endothelin receptor A ($ET_AR$) is observed with advancing PC. Atrasentan is a small molecule that blocks the binding of ET-1 to $ET_AR$, thereby resulting in a decreased function of the osteoblast. In Phase-II and Phase-III clinical trials, atrasentan resulted in different trends regarding the delay in time to disease progression [109, 110]. The Southwest Oncology Group is currently planning a Phase-III trial of docetaxel plus atrasentran versus docetaxel alone.

Most of prostate adenocarcinomas display focal neuroendrocrine (NE) differentiation at diagnosis. NE cells produce peptides, hormones and growth factors which could trigger proliferation, inhibit apoptosis and stimulate neoangiogenesis of the neighboring exocrine PC cells [111]. AIPC cells express a unique subset of somatostatin receptors. Somatostatin analogs have raised considerable interest as potentially useful agents in cancer treatment since they have antineoplastic activity in both in vitro and in vivo models. The primary effect of somatostatin analogs is inhibition of the release of various peptide hormones secreted by NE cells. The combination of ethinyl estradiol and lanreotide had a favourable toxicity profile, and showed objective and symptomatic responses in patients with limited treatment options and refractoriness to conventional hormonal therapy strategies [24].

The selection of molecular targeted agents against cancer depends on the identification of one or few genes involved in both maintenance of the malignant phenotype and cell survival [112]. In Table 1, we list examples of ongoing Phase-II–III in advanced PC divided into three groups targeting, respectively: I. primarily the tumor microenvironment, II. the tumor and bone metastasis microenvironment III. primarily the bone metastasis microenvironment. Finally a suggested paradigm of investigational treatment options for patients with AIPC is presented in Fig. 1.

**Table 1** Examples of ongoing Phase-II–III Clinical Trials in advanced prostate cancer

| Therapy | Target | Phase | Reference |
|---|---|---|---|
| *I. Clinical Trials targeting primarily the tumor microenvironment* | | | |
| Sunitinib/sorafenib | PGDF-R, VEGF-R2,3 | II–III | [95] |
| Genitinib | EGF-R | II | [96] |
| Bevacizumab | VEGF | II-III | [83] |
| Calcitriol | Differentiation cell arrest, apoptosis | II | [103] |
| Histone deacetylase inhibitors | Histone deacetylase | II | [105] |
| Vaccines fowlpox-PSA-TRICOM | PSA, 2nd signal for T-cell activation | II | [83, 85] |
| *II. Clinical Trials targeting the tumor and bone metastasis microenvironment* | | | |
| Oblimersen sodium | BCL-2 mRNA | II | [100] |
| Bortezomib | NF-kB family protein | II | [107] |
| Thalidomide | Antiangiogenic activity | II | [70] |
| J591 antibody | Extracellular epitope PSMA | II | [89] |
| Vaccines | | | |
| Provenge | PAP-activated dendritic cell | II/III | [83] |
| GVAX | PSA and GM-CSF expressing | II/III | [83] |
| Satraplatin | Cytotoxic (microtubule inhibitor) | III | [75] |
| Ixabepilone | Cytotoxic (microtubule inhibitor) | II | [76] |
| Lanreotide | Prostate neuroendocrine cells | III | [24] |
| Vaccines Onyvax-P | Lymph node and bone metastases | II | [84] |
| *III. Clinical Trials targeting the bone metastasis microenvironment* | | | |
| Atrasentan | Endothelin axis | II/III | [110] |

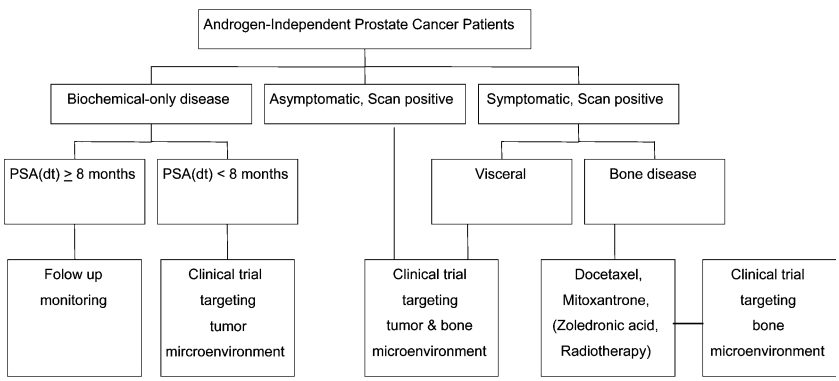


**Fig. 1** Investigational treatment options for patients with AIPC. The compounds are listed in Table 1

## Conclusion and future prospects

Management of advanced PC is plagued by the development of androgen independence. Secondary hormonal manipulation and systemic chemotherapy, especially with docetaxel, are offered to selected patients. Breakthroughs in clinical immunology and molecular biology have allowed novel approaches against AIPC. Vaccination and immunotherapy trials using antibodies, DNA vaccines, recombinant poxviruses, antigen-loaded dendritic cells or transduced allogeneic tumor cells now proceed towards clinical implementation. Targeting angiogenesis and other tumor-promoting processes in the tumor microenvironment and, on the other hand, signal transduction pathways in the malignant cell, are equally powerful and promising approaches under development.

Nowadays, the application of modern genomic technology has begun to facilitate the reclassification of cancers based on their molecular signature. Although patients with a particular type and stage of cancer are often treated as a single group, individualized therapy is being considered, as subsets of these patients who are more likely to benefit from treatment with particular agents are being identified. The challenge today is the development of clinical trials that combine targeted drugs and cytotoxics along with genomic profiling in order to identify subsets of patients

who are most likely to benefit from different therapeutic approaches, thereby avoiding the needless cost and toxicity of ineffective interventions.

In this direction, carefully planned preclinical and clinical studies are required in PC treatment, incorporating extensive molecular characterization. We are now entering a period in which treatment will be based increasingly on the genomic and molecular profile of the individual patient and the specific malignancy. Hopefully, this new era, along with novel pharmaceutical compounds and other innovative approaches introduced in PC management, will improve the outcome of therapeutic manipulations.

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