Treatments for hormonal refractory prostate cancer

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Introduction

Prostate cancer is a leading cause of illness and death among men in Western Europe and the United States. Men with localised prostate cancer have a range of treatment options which include prostatectomy, irradiation and in some cases watchful waiting. In contrast, in metastatic disease, hormonal androgen deprivation therapy has been the mainstay of treatment for many years. Androgen ablation can rapidly lessen bone pain, lead to regressions in soft-tissue metastasis, and reduce serum prostate-specific antigen (PSA) levels. Despite such measures, metastatic tumours progress at a median of 18 to 24 months and the average survival time after which androgen blockade inevitably fails is approximately 12–18 months. For patients who have become refractory to hormonal therapy, new therapeutic strategies are needed.

Molecular biology of prostate cancer

Understanding the underlying molecular biology driving the etiology of prostate cancer and hormonal resistance has provided strategic information as to how prostate cancers arise and progress and to identifying novel therapeutic targets [1]. Most currently available hormonal therapies that interfere with the androgen receptor axis are considered palliative, since hormone unresponsiveness eventually develops.

The androgen receptor plays a critical role in the development of hormone refractory prostate cancer (HRPC). The androgen-receptor gene is the only gene that is consistently up-regulated during tumour progression in different HRPC experimental models [2].

The mechanism of androgen resistance development can be divided into two pathways – those that involve the androgen receptor and those that bypass the receptor [3]. Pathways involving androgen-receptor–mediated survival of prostate-cancer cells include amplification or mutations of the receptor, deregulation of growth factors or cytokines, and alteration of co-activators [4].

In about third of HRPC patients there is amplification of the androgen-receptor gene, which is not present when the tumours are hormone-dependent. This amplification leads to increased expression of the androgen receptor and enhanced activation of the receptor by low levels of androgens. Patients with HRPC and amplification of the androgen- receptor gene survive longer than patients without amplification of this gene [3]. Mutations in the androgen-receptor gene are less frequent and when they occur, they normally increase the number of ligands that can activate the receptor. Thus, a receptor that is normally activated specifically by dihydrotestosterone can, if mutated, respond to other steroids as well as to antiandrogens.

A third pathway that involves the androgen receptor depends on alterations in growth factors such as insulin-like growth factor I and cytokines such as interleukin-6, which activate the receptor. There is an alteration of the function or expression of androgen-receptor co-activators that facilitate activation of the receptor. Several of these growth factors and co-activators are overexpressed in HRPC.

HRPC cells may also use survival pathways that completely bypass the androgen receptor [5]. One pathway is related to the neuroendocrine differentiation of prostate-cancer cells. Neuroendocrine cells are present in prostate stem cells and increase in HRPC. Neuroendocrine cells have a low rate of proliferation, which permits them to survive many different types of treatment. One of the autocrine loops in prostate cancer is the neurotrophn/trk pathway, whereas under normal conditions prostate epithelial cells are dependent of the supply of the soluble growth factors from the stroma, the cancer cells switch on an autocrine loop, the cancer cell expresses a receptor and the growth factor, providing a mechanism for independence from extracellular growth. Neuroendocrine cells secrete neuropeptides such as serotonin and bombesin, which can increase the proliferation of neighboring cancer cells, thereby allowing progression of HRPC. Neuroendocrine cells are present in 40%–100% of patients with HRPC.

One of the lessons learned from the androgen ablative therapies is that apparently interfering with testosterone-binding or overall lowering of serum testosterone is not sufficient to fully block the androgen receptor axis. It is in fact the reason why specific androgen receptor modulators (SARMS) are being considered since they interfere at different levels with the androgen receptor axis [6].

One of the most critical pathways that by passes the androgen receptor involves the deregulation of apoptotic genes. In this regard, the tumour suppressor gene *PTEN* (for phosphatase and tensin homologue) and the antiapoptotic gene *Bcl-2* play important roles in HRPC. PTEN inhibits the phosphatidylinositol 3-kinase pathway in normal cells. Activation of this pathway stimulates a protein called Akt, which inactivates several proapoptotic proteins, thus enhancing cell survival. In the normal prostate, PTEN allows cells to undergo apoptosis, whereas in cancer cells and in HRPC, the loss of PTEN increases Akt activity and blocks apoptosis. Loss of PTEN function is infrequent in androgen-dependent prostate cancer. Inactivation of PTEN is considerably more likely to occur in HRPC. One of the primary targets of Akt, when it is blocking apoptosis, is Bcl-2. Activated Akt frees Bcl-2 (which is bound to a protein called Bad), allowing it to increase cell survival. Overexpression of Bcl-2 has been implicated in the progression to HRPC [7]. Despite these advances in research on prostate cancer, the mechanisms by which a prostate cancer cell survives after androgen-ablation therapy are still not entirely understood.

Chemotherapy in prostate cancer

Docetaxel chemotherapy induces apoptosis by inhibiting Bcl-2. Docetaxel phosphorylates Bcl-2 at serine residues, which inactivates this protein and leads to the activation of the caspase cascade and apoptosis. Docetaxel also inhibits the growth of Bcl-2–negative tumours and is believed to do so by inducing overexpression of the cell-cycle inhibitor p27, which is frequently lost in HRPC.

There has been a change in the clinical management of patients with HRPC based upon the findings of recent phase III studies. The standard of care for HRPC until very recently has been mitoxantrone chemotherapy combined with cortisone. This therapy ameliorates bone pain in about 30% of patients, but it has never been associated with an advantage in survival [8,9]. The results of two independent research teams have revealed that a taxane-based chemotherapy regimen can lead to a survival benefit in men with HRPC.

In a large international trial, two schemes of docetaxel and prednisone were compared to mitoxantrone and prednisone [10]. In the TAX 327 study, 1006 men with HRPC were randomly assigned to docetaxel 75 mg/m^2 every 3 weeks, docetaxel 30 mg/m^2 once per week for 5 weeks, or mitoxantrone 12 mg/m^2 every 3 weeks. All patients also received 5 mg oral prednisone twice daily. Treatment was given for 30 weeks.

Docetaxel given every 3 weeks increased survival by 24% as compared to mitoxantrone and prednisone. The median survival was 18.9 months in the every 3 week docetaxel group, 17.4 months in the weekly docetaxel group and 16.5 months in the mitoxantrone group. Pain reduction was most pronounced in those that received docetaxel every 3 weeks (35% compared with 31% on weekly docetaxel and 22% on mitoxantrone).

Another trial, SWOG 9916, compared docetaxel and estramustine to mitoxantrone and prednisone [11]. Of the 674 patients eligible for the trial, 338 received docetaxel (60 mg/m^2 every 21 days) and estramustine (280 mg 3 times daily over 5 days). The other 336 received mitoxantrone (12 mg/m^2 every 21 days) and prednisone (5 mg twice daily). In an intention-to-treat analysis, the median overall survival was longer for patients receiving docetaxel and estramustine than with mitoxantrone and prednisone, with a 20% reduction in the risk of death in favour of the docetaxel group. Median survival on the docetaxel and estramustine arm was 17.5 months, compared to 15.6 months. The median time to progression was 6.3 months compared to 3.2 months. PSA declines of at least 50% occurred in 1/2 of the patients taking the docetaxel-based regimen, compared to about 1/4 of patients. Grade 3 or 4 neutropenic fevers, nausea and vomiting, and cardiovascular events were more common among patients receiving docetaxel and estramustine than among those receiving mitoxantrone and prednisone.

The studies, while slightly different in design, produced very similar results. A regimen centered on docetaxel can improve survival by a median of 2 to 2.5 months, reducing the risk of death by 20% to 24% in comparison to mitoxantrone. In addition to an improvement in survival, docetaxel was linked to an increase in time to disease progression, in PSA declines, and in quality of life. There was also a confounding high cross-over rate between the two arms in these studies and the studies compared two active regimens. These results are likely to alter our perceptions about the chemoresponsivenesss of

prostate cancer and to alter the standard of care for patients with HRPC.

New chemotherapeutic agents

Epothilones have significant anti-tumour activity in *in vitro* and *in vivo* models that are insensitive or resistant to taxanes. Although reversible neurotoxicity is the predominant toxicity, an advantage is that no corticosteroid premedication is required. Epothilone B analogue (Ixabepilone) was evaulated by the SWOG [12] revealing 34% confirmed PSA responses, and in a multi-institutional trial with or without estramustine, significant clinical activity in HRPC was observed [13,14]. Further studies are warranted to define activity in the second-line setting and perhaps in comparison to standard therapy.

Satraplatin is an orally bioavailable platinum compound with activity against a variety of solid tumours. It exhibits *in vitro* cytotoxicity comparable to cisplatin, and activity against some cisplatin-resistant human tumour lines. In murine tumours and human ovarian cancer xenografts, oral satraplatin had antitumour activity comparable to intravenous cisplatin or carboplatin. In an EORTC Genitourinary Tract Group trial, a >50% reduction in PSA was seen in 8.7% on the prednisone versus 33.3% on Satraplatin with better PFS on the Satraplatin arm [15]. This drug is now being evaluated in an international phase III trial in the second-line setting, a clear need that is still unmet in patients HRPC.

Chemotherapy and targeted therapy

Docetaxel is now being combined with several newer biologic and targeted therapeutic agents. Pretreating HRPC patients with antisense oligonucleotides may make docetaxel more effective. As mentioned previously, Bcl-2 is an important pro-survival regulator of apoptotic cell death. Oblimersen is a phosphorothioate antisense oligonucleotide complimentary to the Bcl-2 mRNA and a potent inhibitor of Bcl-2 expression which in pre-clinical testing can significantly enhance the therapeutic effect of chemotherapy, hormone and radiation therapy. The antisense oligonucleides directed to Bcl-2, Oblimersen Sodium (Genasense) lowers Bcl-2 levels [16]. The EORTC Genitourinary Tract Group is comparing docetaxel to docetaxel plus Oblimersen Sodium in a randomised phase II trial.

Thalidomide and its analogues modulate the immune system in various ways. Some of these immunomodulatory activities, together with the anti-angiogenic, anti-proliferative and pro-apoptotic properties, are believed to mediate anti-tumour responses in some tumours. Another randomised phase II trial combining docetaxel with thalidomide resulted in an encouraging PSA decline rate. At 18 months, overall survival in the docetaxel plus thalidamide group was 68.2% as compared to only 42.9% in the docetaxel alone group [17].

Bone-targeted therapy

HRPC is associated with the development of painful bone metastases. Newer generation bisphosphonates may relieve pain caused by bone metastases, prevent treatment-related loss of bone mineral density, possibly slow the growth of metastases, and reduce skeletal complications. They are effective for the treatment of both osteolytic and osteoblastic metastases.

In a randomised trial, Zoledronic acid (Zometa) reduced the incidence of skeletal-related events (SREs) in patients with HRPC. Patients treated with 4 mg of zoledronic acid as compared to placebo had a significantly lower incidence of SREs, regardless of whether they had an SRE prior to entry in the study [18]. Bisphosphonate therapy has become a standard of care for patients with malignant bone disease.

Endothelin-1, acting via the endothelin-A receptor, has been implicated in the metastasis and progression of prostate cancer, particularly in bone. Atrasentan is a potent, oral, selective endothelin-A receptor antagonist (SERATM). Two large randomised placebo-controlled studies of atrasentan were performed in men with metastatic HRPC with time to disease progression (TTP) as the primary endpoint. Atrasentan 10 mg, resulted in a statistically significant delay in TTP in the protocol-specified analysis of the evaluable population of both studies; however, the delay in TTP did not reach significance in the intent-to-treat patient population of either study ($P = 0.132$ and $P = 0.136$). A meta-analysis of the two randomised controlled studies was conducted [19]. The meta-analysis demonstrated that in men with metastatic HRPC, Atrasentan 10 mg resulted in significant reduction in the risk associated with disease progression; attenuation of the rise of biomarkers PSA and BALP; delay in time to biochemical progression; decrease in time to bone pain and incidence of bone pain; and disease-specific quality of life benefit.

VEGF is a growth factor that is essential for pathological neoplastic angiogenesis, tumour growth and metastasis. Increased levels of VEGF expression have been found in many human tumours [20]. The tumour-associated stroma may also produce significant amounts of VEGF via tumour-associated induction of the VEGF gene promoter. Inhibition of VEGF signalling with several strategies, including monoclonal antibodies to VEGF (Bevacizumab, Avastin; Humanized monoclonal antibody) are currently under clinical development. The Cancer and Leukemia Group B (CALGB trial 9040), Eastern Cooperative Group (ECOG) and the NCIC (National Cancer Group of Canada) are performing a randomised double-blinded placebo controlled phase III trial in 1020 patients comparing docetaxel and prednisone with or without Bevacizumab in patients with HRPC. Patients are stratified according to the Halabi nomogram which is predictive of survival [21].

Vaccine therapy

Prostate cancer cells express many unique differentiation associated antigens which allow for development of organ specific targeted vaccines. APC8015 (Provenge) utilises prostate acid phosphatase (PAP), which is highly expressed in more than 90% of prostate tumours. APC8015 (Provenge) is an immunotherapy cellular product consisting of autologous peripheral blood mononuclear cells enriched for a dendritic cell fraction pulsed with a Prostatic Acid Phosphatase (PAP)-GM-CSF construct. Patients with asymptomatic metastatic HRPC were randomised (2:1) to receive APC8015 (n=82) or placebo (n=45) every 2 weeks $\times 3$. Eligible patients had >25% of cancer cells positive for PAP by central pathology review. The primary endpoint was TTP. Secondary endpoints included TDRP and overall survival (OS); and OS data from this trial were recently presented [22]. There were 127 patients; 34% of those on Provenge were alive compared to 11% in the placebo after 3 years. Patients who took Provenge lived an average 25.9 months compared to 21.4 months (4.5 months more than the placebo arm). In a subset analysis, treatment with APC8015 resulted in a 6.4 month survival advantage in patients with Gleason Scores of $\leqslant 7$ forming the basis for an ongoing pivotal Phase III trial. These results are clearly interesting and provocative.

Conclusions

Advances in the understanding of the molecular mechanisms implicated in prostate cancer progression have identified many potential therapeutic molecular targets. The search for therapies aimed at prolonging life in patients with HRPC is beginning to produce results. We now have a foundation that provides a platform for the translation of novel agents into new combination cancer therapies. In addition to recently completed docetaxel trials, promising new drug combination trials are in progress. New approaches should lead to better therapeutic modalities to combat prostate cancer. Further work must be done to improve our understanding of the pivotal targets which drive prostate cancer and various pathways that are affected in different cancers.

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