introduction

Prostate cancer represents a major health problem. It is the second most common cancer in men worldwide, with an estimated 2.6 million new cases each year in Europe. Prostate-specific antigen (PSA) testing has radically changed practice, as most patients are now diagnosed at an earlier stage when potentially curative treatment is possible. Nonetheless, prostate cancer continues to be the second leading cause of male cancer mortality.

Prostate cancer is generally sensitive to hormonal manipulation at the time of initial diagnosis. Although most patients with advanced metastatic disease initially respond to conventional androgen deprivation with medical or surgical castration, the median duration of disease control is between 13 and 22 months and overall survival is 28–36 months. Patients with metastatic prostate cancer, who have disease progression following primary androgen ablation therapy are generally considered to be refractory to hormonal therapy. The clinical status of patients after failure of castration is commonly referred to as hormone-refractory prostate cancer (HRPC), or androgen-independent prostate cancer (AIPC). Although used widely in clinical settings, the terms HRPC and AIPC do not reflect the biology of advanced prostate cancer where androgen receptor and its ligand remain pivotal in tumour growth. Prostate cancer progression after conventional medical or surgical castration should be considered as castration-resistant prostate cancer (CRPC).

Until 2004, no chemotherapy regimen had been shown to improve survival. Primarily urologists and radiation therapists treated prostate cancer and patients were referred very late to medical oncologists [1].

Chemotherapy can provide palliative benefit. Mitoxantrone and prednisone provide palliative symptom relief in approximately a third of patients [2, 3].

standard chemotherapy in metastatic HRPC

Two large landmark randomized phase III studies with docetaxel-based therapy (TAX 327 and SWOG 9916) have demonstrated a survival benefit with docetaxel chemotherapy for patients with metastatic HRPC [2, 4], setting a new standard of care for this disease. The results of the TAX 327 study have persisted with extended follow-up [5], revealing 19.2 months median survival for every 3-week docetaxel and prednisone treatment as compared to 16.3 months with mitoxantrone and prednisone [hazard ratio (HR) = 0.79, \( P = 0.004 \)] with improved survival in senior adult patients and both asymptomatic and symptomatic patients. Baseline PSA doubling time (PSADT) was found to predict overall survival after chemotherapy [6], as were other factors apart from chemotherapy, which were used in a prognostic nomogram, which predicts survival at 1, 3 and 5 years with modern chemotherapeutic regimens. This multivariate model identified several new independent prognostic factors in men with metastatic HRPC, including PSADT, and led to the success of a clinically applicable nomogram.

Interest in improving upon these results has dramatically increased with the approval of docetaxel for HRPC. In addition, improved understanding of the androgen receptor and of mechanisms responsible for prostate cancer development and progression have led to the discovery of several biologic targets that can be exploited using novel therapeutics.

targeted therapy

Targeted therapy is treatment using agents directed at specific pathways, processes and physiology that may be uniquely disrupted in cancer cells. Prostate cancer is a solid tumour with heterogeneity in histology, gene expression and phenotype between different patients and even within the same patient [7]. It is fundamental that drug development takes advantage of preclinical knowledge in understanding prostate cancer biology. Several research approaches are ongoing, building upon docetaxel by combining docetaxel with targeted agents, investigating novel agents and further exploiting the androgen axis.

A significant limitation in studying this disease is assessing treatment response. Current methodologies are inadequate in assessing response in bone—the predominant site of metastasis in 85–90% of men and often the only site of disease. The radionuclide bone scan is suboptimal for response assessment. As a result, all response criteria, including the
Response Evaluation Criteria in Solid Tumors (RECIST), consider bone to be a 'non-measurable' disease site.

Other imaging modalities are being explored and alternative experimental designs and endpoints to assess response being developed. Whether these are better or more appropriate must still be determined. In addition, PSA is remarkably unreliable in assessing response. A decrease in PSA of 30% after 3 months of treatment has been associated with an improvement in survival [8], but increases may be seen in up to 23% of patents prior to responding to therapy [9]. New guidelines recommend that patients remain on treatment for at least 12 weeks before deciding the effect of therapy [10]. Numerous therapeutic targets and surrogate endpoints are under investigation.

targeting angiogenesis

Angiogenesis is a complex process necessary for tumour growth and metastasis [11]. Modulating or inhibiting angiogenesis can be approached through the use of monoclonal antibodies to vascular endothelial growth factor (VEGF) (bevacizumab), by decoy receptors (VEGF Trap), or small molecule inhibitors. Targeting angiogenesis has proven successful in other tumour types. Aberrant blood vessel formation is associated with anomalies in pathways involved in apoptosis, androgen receptor signalling, signal transduction, cytokine function and cellular adhesion [12]. Increased levels of angiogenic factors have been associated with adverse outcomes in prostate cancer [13–17]. Therefore, targeting angiogenesis is a logical approach to the treatment of metastatic prostate cancer.

Bevacizumab is a humanized monoclonal antibody directed against VEGF that has shown significant clinical benefit in several tumour types. In a Cancer and Leukemia Group B (CALGB) trial, bevacizumab (15 mg/kg every 21 days) was given with docetaxel and estramustine to 79 patients with HRPC [18]. A ≥50% decrease in PSA was reported in 81% of patients with a median time-to-progression (TTP) of 9.7 months and median survival of 21 months [19]. This provided the rationale for a phase III trial by the CALGB (90401) of docetaxel and prednisone ± bevacizumab in metastatic HRPC. The primary endpoint is overall survival. To date, 1020 men have been randomized to detect an improvement in median survival from 18 to 22 months.

Aflibercept (AVE0005 or VEGF Trap) is a newly developed VEGF-blocking agent with a stronger affinity and broader activity than bevacizumab [20]. It is a recombinant fusion protein consisting of human VEGF receptor extracellular domains fused to the Fc portion of human immunoglobulin (Ig) G1 (IgG1). It contains sequences encoding Ig domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of the human IgG1 Fc domain. Aflibercept has a much higher VEGF-A binding affinity (0.5 pM dissociation constant for VEGF165 and VEGF121) than a humanized monoclonal antibody. Aflibercept also binds VEGF-B plus factors placental growth factor (PIGF)1 and PIGF2, which may be advantageous in some settings (e.g. malignant ascites where PIGF may mediate vascular permeability).

VENICE is the acronym for a multicentre, randomized, double-blind study comparing docetaxel + prednisone + aflibercept versus docetaxel + prednisone + placebo in a 1:1 fashion in 1200 patients. Patients are stratified according to performance status (PS). The primary endpoint is overall survival. Secondary objectives include PSA response, pain response, time to occurrence of skeletal-related events (SRE), progression-free survival (PFS), response rate, PSA-PFS, pain-PFS, health-related Quality of Life (HRQL) and safety.

targeting bone

the endothelin axis

Activation of the endothelin A receptor (ETA) by endothelin-1 (ET-1) mediates events that regulate mitogenesis, apoptosis, angiogenesis and metastasis. ET-1, a key component of the endothelin axis, plays an important role in the pathophysiology of prostate cancer; particularly in the development and progression of osteoblastic bone metastases [21–24]. The ET-1/ETA receptor pathway is deregulated in prostate cancer and is crucially implicated in proliferation, invasion, escape from apoptosis, abnormal osteogenesis and alteration of nociceptive stimuli [25]. Specific blockade of ETA may have anticancer effects, while retaining beneficial endothelin B receptor (ETB)-mediated effects such as apoptosis and clearance of ET-1.

Atrasentan is an orally bio-available agent that targets the ET-1/ETA pathway by selectively inhibiting the ETA receptor. Following a randomized placebo controlled, phase II trial, which revealed suppression of bone turnover markers paralleling delay in TTP [26], a phase III trial was initiated with atrasentan 10 mg/day versus placebo [27]. The primary endpoint was TTP, with bone scans performed every 12 weeks. The study was closed early after an unexpectedly high number of early progressions, suggesting that atrasentan would not be of benefit when compared with control. Of note, over 50% of patients progressed within 100 days of trial entry, mostly due to bone scan progression. An analysis of the 809 patients accrued prior to trial closure showed a non-significant trend towards an increase in TTP favouring the atrasentan arm. When the analysis was limited to patients with bone metastases, a significant increase in TTP was observed [28, 29]. The study required bone scans every 3 months and found early radiologic progression in the absence of clinical symptoms. It is unclear if performing the frequent bone scans was responsible for removing patients prematurely. Additional support for meaningful clinical activity came from a combined analysis of the 1002 patients from the phase II and III trials randomized to the 10 mg/day of atrasentan or placebo, showing a statistically significant delay in TTP, time to bone pain, as well as time to PSA progression and bone alkaline phosphatase progression compared with placebo [27].

A phase III trial is evaluating docetaxel + atrasentan as compared to docetaxel + placebo with regards to overall survival and PFS. Patients are required to have bone metastases. For patients with progression by bone scan only, treatment will continue until progression is confirmed. PSA progression does not constitute a progression endpoint in this study.

ZD4054 is another orally active agent that selectively targets endothelin A [30]. In a double-blind phase II trial, 312
pain-free or mildly symptomatic HRPC patients with bone metastases were randomized to receive ZD4054 (15 or 10 mg/day orally) or daily placebo [31]. Although PFS was the primary endpoint, and no significant difference was seen, a significant difference in overall survival was observed. Median overall survival was 23.5 months for patients treated with 15 mg [HR 0.65; 95% confidence interval (CI) 0.49–0.86, \( P = 0.052 \)], 24.5 months for those treated with 10 mg ZD4054 [HR 0.55; 95% CI 0.41–0.73, \( P = 0.008 \)] and 17.3 months for the placebo-treated patients.

These provocative results have led to three clinical trials, which comprise the ENTHUSE programme. Study 15 is for HRPC patients with rising PSA only and no metastases. It is intended that 1500 patients will be randomized between ZD4054 or best supportive care. Study 14 evaluates patients with HRPC and osseous metastases who are pain-free or mildly asymptomatic with rising PSA. The trial also randomizes between ZD4054 and placebo and should enroll 580 patients. Study 33 is similar to the SWOG study outlined above. A total of 1044 symptomatic and asymptomatic metastatic HRPC progressive disease (defined by PSA) patients will be randomized between ZD4054 and docetaxel versus docetaxel and placebo. Overall survival is the primary endpoint.

**targeting the vitamin D receptor**

Calcitriol is the most biologically active metabolite of vitamin D. Preclinical prostate cancer studies have shown anti-neoplastic activity of calcitriol and its analogues [32]. Promising preclinical data led to phase I and II studies, which showed that the anti-neoplastic activity of calcitriol occurs at doses substantially higher than physiologic levels.

DN-101 is a high-concentration oral formulation of calcitriol. The ASCENT trial sought to confirm the phase II data with weekly docetaxel and calcitriol. In this double-blind, randomized phase II trial, 250 patients with metastatic HRPC were randomized to weekly docetaxel + DN-101 or docetaxel + placebo [33]. The difference in primary endpoint of PSA decline between the two arms was not statistically significant: 58% with DN-101 + docetaxel versus 49% with docetaxel + placebo (\( P = 0.16 \)). An impressive overall survival difference was observed with an estimated 24.5 months (median survival not yet reached) for DN-101 + docetaxel versus 16.4 months with placebo + docetaxel (HR 0.67; 95% CI 0.45–0.97; \( P = 0.04 \) in multivariate analysis). Grade 3/4 adverse events were less common in the DN-101 arm (58% versus 70%; \( P = 0.07 \)) [33]. A larger phase III trial (ASCENT II) was initiated to confirm these results but was stopped due to an increased death rate in the experimental DN-101 arm.

**Src inhibition**

New approaches target critical signalling molecules and pathways that contribute to tumour growth after resistance to hormonal therapy. Complex interactions of the androgen receptor with other signalling pathways contribute to hormonal resistance. Src family kinases (SFK), platelet-derived growth factor receptor-\( \beta \) (PDGFR-\( \beta \)), c-KIT, focal adhesion kinase (FAK), and EphA2 are receptor tyrosine kinases (TKIs) found to be constitutively activated, over-expressed or activated by the androgen receptor in prostate cancer.

Dasatinib is a potent oral TKI, targeting BCR-ABL and Src-family kinases, EphA2, c-KIT and PDGFR-\( \beta \). Anti-proliferative and anti-osteoclastic activity observed in dasatinib pre-clinical models support the potential of dasatinib as a targeted therapy for prostate cancer [34, 35].

A phase II study is investigating the activity of dasatinib in patients with metastatic HRPC. The primary endpoint is response rate. Owing to the possible multiple mechanisms of action, this is a composite of PSA and bone scan responses and disease control by RECIST. Urinary N-telopeptide (UNTx) was determined every 4 weeks as a measure of bone metabolism. Preliminary results in 46 patients will be presented at the ASCO 2008 meeting [44].

**second line therapy**

Once prostate cancer progresses after failing docetaxel-based therapy, there is no treatment that has been proven to improve survival. Thus, new therapies are urgently needed.

**satraplatin**

Satraplatin is a novel, orally bioavailable platinum compound with activity against a variety of solid tumours as well as cell lines resistant to taxanes, anthracyclines and other platinum compounds.

In a randomized trial of 50 chemo-naive HRPC patients conducted by the European Organization for Research and Treatment of Cancer (EORTC 30972) [36], PFS doubled in the satraplatin + prednisone arm compared with the placebo + prednisone arm (\( P = 0.023 \)). A >50% decrease in PSA was seen in 33% of patients in the satraplatin arm compared to 9% (\( P = 0.046 \)) in the placebo arm. This led to a 950-patient international phase III study, the SPARC trial (Satraplatin and Prednisone Against Refractory Cancer) comparing satraplatin + prednisone to prednisone + placebo as second-line therapy in metastatic HRPC. The primary endpoint was PFS and overall survival. Secondary endpoints included time to pain progression. Other pre-specified endpoints included pain response, tumour response and PSA response. Preliminary results of this trial (\( n = 950 \)) were presented at the 2007 ASCO Annual Meeting [37]. A 33% improvement in PFS in favour of the satraplatin arm was reported (11.1 versus 9.7 weeks; HR 0.67; 95% CI 0.57–0.77; \( P = 0.0000003 \)). All other pre-specified endpoints were statistically significant in favour of satraplatin. Satraplatin was well tolerated although there was more hematologic toxicity in the satraplatin arm. Less than 5% of patients experienced grade 3–4 non-hematologic events. Unfortunately, this drug failed to achieve a difference in overall survival; its approval is under evaluation by the European Medicines Agency (EMEA).

**targeting the androgen receptor**

The androgen receptor has been the most successful target identified in the treatment of prostate cancer. Efforts at further exploitation of the androgen receptor are important. During
‘androgen independent’ progression, prostate cancer cells develop a variety of cellular pathways to survive and flourish in an androgen depleted environment. Postulated and documented mechanisms include androgen receptor gene amplification and mutation, involvement of co-regulators, ligand-independent activation and involvement of tumour stem cells. Identification of these pathways has provided opportunity to investigate specific therapeutics based on these mechanisms.

In the castrate state, ligands to the androgen receptor are thought to be derived primarily from the adrenal glands. Conventional androgen deprivation therapy removes 90% of circulating androgens produced in the gonads. As much as 10% of circulating testosterone remains, in part due to the peripheral conversion of adrenal steroids to testosterone. In addition, androgen levels in the microenvironment of prostate cancer may be maintained in spite of reduced systemic levels. Androgens might be sequestered by prostate tissue [38].

In patients with castrate levels of testosterone, the tissue levels of dehydroepiandrosterone, dihydrotestosterone and androstenedione all remain sufficient to activate the androgen receptor. Furthermore, the androgen receptors are predominately located in the nucleus in biopsy tissue, indicating ligand-binding and the activation of androgen-dependent gene expression. Increased expression of the androgen receptor is common in advanced prostate cancer, and allows lower ligand levels to more strongly activate the androgen receptor.

In a recent publication the observation was made that in high-risk primary prostate tumours and in metastatic biopsies, CYP17A1 gene expression is highly up-regulated [39], suggesting the possibility of in situ production of androgens as autocrine or paracrine growth factors despite castration. Although these preliminary findings require further corroborating evidence, the need to suppress androgen levels in the microenvironment of prostate cancer may be maintained in spite of reduced systemic levels. Androgens might be sequestered by prostate tissue [38].

Abiraterone acetate (CB7630) [17-(3-pyridyl)androsta-5,16-dien-3β-ol] is a steroidal inhibitor of CYP17. Abiraterone was developed as an irreversible inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase), blocking two important enzymatic activities in the synthesis of testosterone, based on the observation that non-steroidal 3 pyridyl esters based on the observation that non-steroidal 3 pyridyl esters improved selectivity for inhibition of 17α-hydroxylase/C17,20 lyase. Pharmacodynamic studies have demonstrated that abiraterone effects on adrenal steroid synthesis are consistent with its mechanism of action. Antitumour effects were evident with PSA response and durable objective responses using RECIST criteria in phase I/II trials [40, 41].

A state of mineralocorticoid excess could occur after pharmacologic inhibition of CYP17, resulting in hypertension, hypokalemia and fluid retention as a result of a compensatory adrenocorticotropin hormone (ACTH) surge secondary to reduced cortisol levels. These side effects are managed with potassium supplementation, eplerenone (selective mineralocorticoid antagonist), anti-hypertensive agents and low dose corticosteroids. A phase III randomized, double-blind, placebo-controlled study of abiraterone acetate (CB7630) in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy will shortly be initiated. The primary objective of the study is to evaluate the treatment effect of abiraterone acetate + prednisone on overall survival compared with placebo + prednisone in patients with metastatic CRPC who have failed one or two chemotherapy regimens, one of which contains docetaxel. The planned sample size of 1158 patients (772 on abiraterone acetate and 386 on placebo) will provide 85% power to detect a difference between a median survival of 15 months in the abiraterone acetate group and a median survival of 12 months in the placebo group (HR = 0.80).

targeting bone

It is now widely understood that the molecular triad of receptor activator of NFκB ligand (RANKL), its receptor RANK and the endogenous soluble RANKL inhibitor, osteoprotegerin (OPG), plays direct and essential roles in the formation, function and survival of osteoclasts. Osteoclastic bone resorption contributes to the majority of skeletal sequelae or SREs in patients with bone metastases [42].

RANKL binds the RANK receptor on osteoclasts or osteoclast precursors to stimulate or promote differentiation into osteoclasts, respectively. This increased osteoclastic activity results in significant skeletal morbidity, i.e. SREs in patients with bone metastases. Including those from prostate cancer [43].

Denosumab is a fully human monoclonal antibody with a high affinity and specificity for RANKL that can bind and neutralize the activity of human RANKL similar to the action of native osteoprotegerin (OPG) and its engineered variants. A randomized, double-blind phase III multicentre study is evaluating denosumab compared with zoledronic acid (Zometa®) in the treatment of bone metastases in men with HRPC. The study is designed to determine if denosumab is non-inferior to zoledronic acid with respect to the first on-study occurrence of a SRE. Secondary objectives are to evaluate if denosumab is superior to zoledronic acid. Approximately 1700 subjects will be randomized in a 1:1 ratio.

collusions

Docetaxel chemotherapy is the standard therapy for patients who have failed initial androgen deprivation therapy. A great deal of progress has been made in understanding the biology of this disease, which has led to a variety of novel agents and therapeutic strategies. The challenge is to improve upon the results with docetaxel and to develop new effective therapies, given the heterogeneous nature and biology of this disease.

disclosures

No significant relationships.

references


27. James ND, Borre M, Zonnenberg B et al. ZD4054, a potent, specific endothelin A receptor antagonist, improves overall survival in pain-free or mildly symptomatic patients with hormone-resistant prostate cancer (HRPC) and bone metastases. Eur J Cancer 2007 (Suppl 5): (Abstract).


