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REVIEW ARTICLE

Broadening horizons in medical management of prostate cancer

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Abstract

Hormonal therapy. Testosterone suppression achieved either medically or surgically is the standard initial treatment for men with advanced prostate cancer. Most men respond but the disease progresses after a median of 1–2 years. Clinical trials suggest that intermittent androgen deprivation therapy (ADT) provides equal or longer time to castration-independence than continuous ADT, and is preferred, especially since there are subtle long-term toxicities associated with ADT. Further hormonal manipulations (including addition and withdrawal of peripheral antiandrogens, steroid synthesis inhibitors such as ketoconazole, and estrogens) can be transiently effective in selected patients with castration-resistant prostate cancer (CRPC). Androgen-dependent signalling pathways remain active in most men with CRPC and are associated with mutation, changes in expression or modulation of the androgen receptor (AR); abiraterone acetate and MDV3100 are promising drugs being evaluated in clinical trials that may lead to further hormonal response. *Chemotherapy*. Eventually men who progress rapidly, are symptomatic, and/or develop metastasis to visceral organs require chemotherapy. Three-weekly docetaxel with prednisone has been shown to improve survival and relieve symptoms but eventually men develop progressive disease or become intolerant to docetaxel. Multiple trials are evaluating new drugs (mainly molecular targeted agents) either given first line with docetaxel chemotherapy, or to men who have progressive disease after receiving docetaxel. Cabazitaxel was shown recently to improve survival as compared to mitoxantrone when used second line and has been approved by the United States Food and Drug Administration (FDA). *Conclusion*. Despite major advances, treatment of men with advanced CRPC remains a challenge both for the seeker and giver of care.

Dr. Charles Huggins was awarded the 1966 Nobel prize in physiology and medicine for his discovery in the 1940s that hormones (specifically estrogens that led to decreased testosterone) could control the spread of prostate cancer. Orchiectomy became a standard treatment (since estrogens were associated with cardiac toxicity) and in the 1980s Leutinising Hormone Releasing Hormone (LHRH) agonists were introduced as a medical alternative. Medical or surgical castration remains the standard initial treatment for men with advanced prostate cancer. Despite clinical and biochemical response in $>$ 80% of patients, mean duration of response to initial androgen deprivation therapy (ADT) is around 18 to 24 months, but is highly variable depending on the biological behaviour of the tumour. Some men with castration-resistant prostate cancer (CRPC) may respond transiently to further hormonal manipulations but eventually become resistant. Current standards for managing these patients and evolving treatment strategies are described below.

Hormonal treatment

Two variants of initial ADT have been investigated in multiple randomised trials: combined androgen blockade (CAB) and intermittent hormonal therapy. Studies have shown that initial CAB (orchiectomy or LHRH agonist with a peripheral anti-androgen) adds cost and toxicity without meaningful benefit as compared to monotherapy or surgery alone [1] and this strategy should not be used. In contrast, emerging data support the use of intermittent ADT, which is based on preclinical observations that intermittent suppression of testosterone delays the time to castration independence in animal models [2]. Several trials have confirmed that intermittent ADT, in which therapy is interrupted when the serum PSA falls to a low value and is reintroduced when it rises above

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a certain level, provides equal or superior duration of disease control compared with continuous ADT [3]. Intermittent ADT can now be regarded as standard treatment for men with a good initial response to treatment, especially as there are evolving data showing subtle long-term toxicities associated with ADT, including bone loss, metabolic syndrome and cardiac events [3–5] (Table I).

Awareness of the chronic toxicities associated with ADT that are summarised in Table I should lead to caution in introducing such therapy, especially in men with predisposing factors, such as a history of diabetes or cardiovascular events. While men with metastatic disease who are symptomatic or have a rapidly rising PSA should be treated, there is no evidence to support initiation of ADT in men with slowly rising PSA after initial local therapy, or those with slowly progressive asymptomatic disease. All men on ADT should be evaluated for bone density, with routine co-administration of calcium and vitamin D, and selective use of bisphosphonates in those with continuing bone loss [4].

Some men whose disease is progressing after primary ADT may achieve further transient response by adding a peripheral anti-androgen. About 20% of those that respond to addition of an anti-androgen may respond to its withdrawal, because the classical agents (flutamide, bicalutamide and nilutamide) can initially inhibit but subsequently stimulate the androgen receptor (AR) [6]. Further responses to hormonal manipulations can be obtained in some men by treatment with agents that inhibit synthesis of adrenal androgens (e.g. ketoconazole used with hydrocortisone), estrogens, glucocorticoids, and by switching from one peripheral anti-androgen to another.

Androgen-dependent signalling in men with CRPC

Despite the high rate of initial response, men eventually develop resistance to the above forms of hormonal therapy via mechanisms that include persistent signalling through the AR, mutation or changes in the expression or modulation of the AR, and activity of alternate cellular pathways that stimulate proliferation of prostate cancer cells [7]. Even in the castrate state, substantial levels of androgens may be produced within prostate tumour tissue and can stimulate the AR [8]. Around one quarter of prostate cancers in men with CRPC have been reported to carry a point mutation, especially Thr-Ala877 [9], resulting in activation by commonly used hormonal agents such as peripheral anti-androgens and estrogens. The AR-dependent signalling pathways have also been shown to cross talk with other growth signalling pathways in prostate cancer cells including those dependent on epidermal growth factors, vascular endothelial growth factor, fibroblast growth factors and transforming growth factor, thereby leading to mechanisms of cell survival despite the castrate state [7]. Two novel agents that target AR-associated signalling in men who are resistant to current forms of hormonal manipulation, abiraterone acetate and MDV 3100, are being evaluated in Phase III clinical trials.

Table I. Toxicities associated with ADT reported in clinical trials.

- Decrease in bone mineral density, leading to increased risk of fracture
- Loss of muscle mass
- Increase in body fat, especially abdominal subcutaneous fat
- Gynecomastia
- Impotence
- Hot flashes and symptoms of male menopause
- Anaemia
- Increased risk of diabetes
- Increased risk of coronary artery disease
- Increased risk of sudden cardiac death

Abiraterone acetate. Abiraterone acetate (hereafter 'abiraterone') is an orally active compound that functions by irreversibly inhibiting enzymatic activity of 17-alpha mono-oxygenase (17 alpha-hydrolase/C17,20 lyase complex), a member of the cytochrome p450 family. This enzyme catalyses the 17-alpha hydroxylation of steroids, required in two key steps for the conversion of cholesterol to androgens. Hence, abiraterone suppresses androgen synthesis in the testis, the adrenal glands and in other sites, including prostatic tissue. Abiraterone is reported to be well tolerated with easily managed side effects such as hypertension and kypokalemia, which can be reduced by co-administration of low-dose prednisone. In a multinational Phase II trial [10], which recruited 58 men with CRPC after docetaxel chemotherapy, abiraterone was associated with PSA response (i.e. 50% or greater maximal decline) in 43% of men including 30% of those pretreated with ketoconazole and 55% who were ketoconazole-naïve. Another post-chemotherapy Phase II trial reported PSA response in 24 (51%) of 47 patients. In both these trials treatment with abiraterone was associated with reduction in circulating tumour cell (CTC) counts – a marker reported to be predictive of survival of men with metastatic CRPC [11]. High baseline serum levels of dehydroepiandrostenedione (DHEA), DHEA-sulfate (DHEA-S) and estradiol have been recognised as markers predicting biochemical response and time to progression after abiraterone [12]. Large multinational Phase III studies have completed recruitment including a double-blind placebo-controlled trial of abiraterone and prednisone versus prednisone alone in men with CRPC who have progressed after receiving docetaxel, and a related trial for chemotherapy-naïve men with CRPC who were minimally symptomatic.

MDV3100. MDV3100 is an orally available potent antagonist of the AR that inhibits nuclear translocation, co-activator peptide recruitment and DNA binding, and lacks agonist activity [13]. A Phase I/II study in 140 men with progressive CRPC showed an impressive PSA response rate in 57% (37/65) of chemotherapy-naïve men and 45% (22/49) in men who had received chemotherapy [14]. The authors also reported that 92% of patients who had CTC counts < 5 (favourable) at baseline maintained favourable CTC counts post-treatment and 53% (21/40) of those with > 5 CTC (unfavourable) converted to favourable CTC counts post-treatment, indicating a promising role of this agent in treatment of prostate cancer. A Phase III placebo-controlled trial with 2:1 randomisation in favour of MDV3100 in the post-chemotherapy setting is underway with overall survival as the primary endpoint.

Chemotherapy

Mitoxantrone, used with low-dose prednisone, was the first chemotherapy drug approved for treatment of men with CRPC, on the basis of improvement in symptoms (especially pain) in randomised trials compared to prednisone alone [15,16]. Mitoxantrone has the advantage of low toxicity, provided the total dose is limited to prevent cardiac toxicity, and is well tolerated even by very old men. There were no trends to improved survival in the mitoxantrone trials, although they were too small to detect them. Subsequently the TAX-327 trial demonstrated that docetaxel, given every three weeks at 75 mg/m^2 with prednisone 5 mg bid prolonged overall survival of men with CRPC by about three months, as compared to mitoxantrone and prednisone, and improved the quality of life of symptomatic men [17]. Surprisingly weekly docetaxel was not as effective, and not less toxic, in the 3-arm TAX327 trial. The SWOG 99-16 trial [18] compared docetaxel and estramustine with mitoxantrone and prednisone: it also showed a small benefit for the docetaxel arm, but together these trials suggest that estramustine adds toxicity without benefit, and there is no basis for the continued use of this drug. Only about half of men with CRPC respond to docetaxel chemotherapy, and all of them eventually discontinue this treatment because of toxicity or disease progression.

There are multiple causes of resistance to taxanes including cellular causes related to drug uptake and retention in cells, and changes to its binding to and action to stabilise β-tubulin. The drug may also have limited distribution within solid tumour tissue. Preclinical evidence has suggested that taxanes exert their antineoplastic activity in prostate cancer partly by blocking AR signalling [19], so that overexpression, amplification and mutation of the AR may also play a role in the development of a chemo-resistant state [20].

New types of chemotherapy, and molecular targeted agents are being (or have been) evaluated with the goal of either enhancing the effectiveness of docetaxel when used in combination, or of providing further benefit when used in men whose disease has progressed during or after treatment with docetaxel. Some of these agents are described below.

Second-line chemotherapy

Retreatment with docetaxel. For men with CRPC who demonstrate clinical and/or biochemical response to docetaxel as first-line chemotherapy, followed by a period off-treatment, re-introducing docetaxel is a reasonable option if the treatment was tolerated well.

Mitoxantrone. About 15% of men with CRPC respond to mitoxantrone after progressing on docetaxel [21], and given the excellent tolerance of this agent, it is a reasonable choice of second-line chemotherapy in symptomatic men with acceptable cardiac function.

Satraplatin. Satraplatin is a third generation oral platinum compound which had shown activity in a Phase II trial. Consequently, a large ($n = 950$) randomised Phase III clinical trial compared satraplatin to placebo, each with low-dose prednisone in men with CRPC after first line chemotherapy (only about half of the participants had received docetaxel) [22]. Risk of disease progression was reduced by satraplatin (Hazard Ratio, $HR = 0.67$; $p < 0.001$) with significant reduction in time to pain progression but there was no difference in overall survival. The FDA and European Medicines Agency (EMEA) did not approve this drug for use in men with prostate cancer.

Cabazitaxel. Cabazitaxel is a semi-synthetic derivative of the natural taxoid 10-deacetylbaccatin III and like docetaxel acts by binding and stabilising tubulin, resulting in the inhibition of microtubule depolymerisation and cell division, cell cycle arrest in the G2/M phase, and the inhibition of tumour cell proliferation. It differs from other taxanes in that it is a poor substrate for the membrane-associated, multidrug resistance, P-glycoprotein efflux pump and crosses the blood-brain barrier. A recent randomised controlled trial compared cabazitaxel (25 mg/m^2) with mitoxantrone (12 mg/m^2), each given with prednisone (10 mg/day) as second line

chemotherapy in 755 men with CRPC who had received docetaxel [23]. There was a statistically significant difference in overall survival favouring cabazitaxel (HR = 0.70, p = 0.0001) with an increase in median survival of about 2.5 months. This led to approval of cabazitaxel by the FDA and the drug will probably also be approved by EMEA. However, this drug may exacerbate peripheral neuropathy, a common residual side effect in men post-docetaxel – so that careful selection of patients will be crucial. Also, there was a ~5% rate of toxic death in the cabazitaxel arm of the randomised trial that might have been reduced by administering a lower dose. A full article describing this trial is awaited, and should address how long after treatment with docetaxel the patients were enrolled; as described above, many patients who respond initially to docetaxel and have a break from treatment may benefit from re-treatment with docetaxel.

Ixabepilone and patupilone. Ixabepilone and patupilone are water soluble epothilones with a related mechanism of action to taxanes. They exhibit their anti-neoplastic activity primarily by inhibition of microtubule formation. A randomised Phase II trial comparing ixabepilone and mitoxantrone with prednisone in docetaxel pre-treated men demonstrated PSA response rates of 17% and 20% respectively and overall survival of 9.8 months in the entire cohort [24]. Given this disappointing result, it seems unlikely that ixabepilone will be studied further in men with CRPC.

A Phase II study of patupilone in 45 patients (55% had previous taxane therapy) was well-tolerated but only 13% of patients had a PSA response and the median overall survival was 13.4 months [25]. A multicentre Canadian study evaluating patupilone in CRPC after first line docetaxel is planned.

Molecular targeted agents

Multiple targeted agents have been evaluated in Phase II trials at various stages of disease in men with CRPC, and some of them have been (or are being) evaluated in Phase III randomised trials to determine whether they augment the activity of docetaxel. These trials are described briefly below. However, as yet no molecular targeted agent (other than those acting via hormonal mechanisms) has shown sufficient activity to warrant approval for treatment of men with prostate cancer.

Inhibitors of angiogenesis. Formation of blood vessels is a requirement for growth of solid tumours including prostate cancer, and agents targeting angiogenesis are being evaluated. Bevacizumab, a monoclonal antibody blocking Vascular Endothelial Growth Factor-A (VEGF-A) has been approved for use with chemotherapy in people with advanced colorectal and lung cancer, on the basis of small improvements in survival. A recent randomised controlled trial evaluated bevacizumab with docetaxel and prednisone for men with CRPC but did not show a significant survival difference as compared to docetaxel and prednisone alone [26].

A large trial comparing docetaxel and prednisone with or without aflibercept, a potent inhibitor of VEGF-A, VEGF-B and placental growth factor, has completed accrual. Other inhibitors of angiogenesis such as sunitinib, and thalidomide and its analogues (e.g. lenolidamide), have shown activity in Phase II clinical trials in men with CRPC [27,28]. Randomised Phase III clinical trials evaluating sunitinib in post-chemotherapy patients and lenalidomide in combination with docetaxel are underway. One problem with this approach might be the presence of redundant pathways that may stimulate angiogenesis, such that inhibitors of only one pathway may have limited effects.

Inhibitors of Endothelin-A. Endothelin-A antagonists are reported to exhibit antitumour properties mainly by inhibition of cell proliferation, induction of apoptosis, decrease in osteoclastic bone resorption and inhibition of VEGF. However a randomised trial evaluating atresantan, an orally available inhibitor of endothelin-A did not meet its endpoint of time to disease progression in men with CRPC [29]. ZD4054, another Endothelin-A antagonist, is being evaluated in a randomised Phase III clinical trial in non-metastatic CRPC with dual primary end-points of progression-free survival and overall survival.

Apoptotic pathways. Some agents that are known to stimulate apoptosis have been evaluated in combination with chemotherapy for men with CRPC. Custirsen (OGX-011), an antisense oligonucleotide targeting clusterin gave encouraging results in a Phase II clinical trial in combination with docetaxel [30] leading to an ongoing Phase III clinical trial. Gataparsen sodium, an antisense oligonucleotide targeting survivin, and AT-101, an oral, pan-Bcl-2 inhibitor are being evaluated in Phase II clinical trials in combination with docetaxel and prednisone.

Inhibitors of other pathways. Agents targeting cell-survival pathways that have cross-talk with AR-dependent pathways have been evaluated in early phase clinical trials but the results are generally

disappointing. Studies of inhibitors of epidermal growth factor receptors (EGFR1 and 2; e.g. erlotinib, gefitinib, trastuzumab and pertuzumab) alone or in combination with docetaxel have not been encouraging. Similarly, the anti-interleukin-6 monoclonal antibody siltuximab (CNTO 328) led to increased mortality when combined with mitoxantrone as compared with mitoxantrone alone and the trial was prematurely terminated [31]. Despite discouraging results using targeted monoclonal antibodies, others including cetuximab, cixutumumab and figitumumab are being evaluated in Phase II clinical trials. A study of TKI258, an inhibitor of fibroblast growth factor (FGF) is recruiting men with CRPC focused at evaluating markers of FGF signalling in bone marrow and plasma.

Additional strategies

Immunomodulation. Men diagnosed with prostate cancer are generally old and may have multiple co-morbidities leading to poor tolerance of cytotoxic chemotherapy. Immuno-modulation might be a preferable treatment strategy for these men. Two Phase III clinical trials evaluated administration of a vaccine (GVAX) consisting of two allogeneic prostate cancer cell lines (PC3 and LNCaP) ,which were genetically modified through adenoviral transfer to secrete granulocyte macrophage–colony-stimulating factor and lethally irradiated. Two randomised trials comparing GVAX to docetaxel/prednisone (VITAL1) and GVAX + docetaxel/prednisone to docetaxel/prednisone (VITAL2) failed to meet their primary end-point of an increase in survival and were terminated prematurely [32,33]. In a novel but complex approach, dendritic cells were taken from patients, transported to a centre where they were exposed to prostatic acid phosphatase (PAP), and transported back to be re-infused into the patient. A recent Phase III randomised clinical trial evaluating this approach (known as Sipuleucel-T) in men with metastatic CRPC demonstrated a significant survival advantage over placebo (median survival 25.8 versus 21.7 months; hazard ratio 0.78; $p = 0.03$) [34]. This led to approval of this vaccine by the FDA (not yet by EMEA). There may however be challenges in bringing such agents into clinical practice because of the cost and logistics associated with the production process.

Bisphosphonates and Denosomab. Bone metastasis in CRPC is associated with RANKL-mediated osteoclast activation [35]. The potent bisphosphonate, zoledronic acid has demonstrated an effect to delay the time to skeletal related events (SREs: defined by time to pathologic fracture of the bones, need for surgical/radiotherapeutic intervention or spinal cord compression) in men with CRPC and bone metastasis [36]. More recently, a fully human monoclonal antibody against RANKL, denosumab was compared with zoledronate in a Phase III randomised controlled clinical trial with 1901 patients. There was delayed time to first SRE in favour of denosumab [37], but overall survival and time to cancer progression were similar and more frequent adverse events such as osteonecrosis of the jaw and hypocalcemia were seen in the denosumab arm. It seems unlikely that this (undoubtedly expensive) agent will provide substantial benefit compared to standard bisphosphonates.

Analogues of vitamin D. After a Phase II trial (ASCENT) [38] with favourable PSA-response and survival with high-dose calcitriol (DN-101) as compared to placebo in combination with docetaxel, a Phase III clinical trial (ASCENT-2) was designed. However interim analysis after randomisation of 953 patients revealed inferior survival in men receiving DN-101 with docetaxel than those receiving docetaxel alone [39]. Median overall survival was 16.8 months for DN-101 subjects and 19.9 months for controls (HR = 1.33; $p = 0.019$) and hence the trial was terminated prematurely.

Radioisotopes. The bone-seeking radioisotopes, ^{89}Strontium and ^{153}Samarium are useful for palliation of pain in men with CRPC and widespread bone metastases, although they may suppress bone marrow function and increase the toxicity of subsequent chemotherapy. ^{89}Strontium was reported to show substantial survival benefit (27.7 months versus 16.6 months, $p = 0.001$) when given as consolidation treatment post-chemotherapy in a Phase II study of men with CPRC and bone metastases [40], and is being evaluated in a randomised Phase III clinical trial. Similarly, the combination of ^{153}Samarium with docetaxel in a Phase II study for men with CRPC and bone metastases was well tolerated, and showed long-lasting pain control and favourable survival [41]. Encouraging results were also reported with ^{223}Radium in a randomised Phase II study [42]; a randomised Phase III trial of radium-223 versus placebo in men with symptomatic bone metastates from prostate cancer is underway.

In summary, drug development aimed at improving survival and its quality for men with advanced prostate cancer is a very active area of preclinical and clinical research that includes strategies involving hormonal agents, classical chemotherapy, molecular targeted agents, bone seeking radio-isotopes and immune modulation.

Declaration of interest: Dr Tannock has advised several companies about prostate cancer trials and has also chaired such trials. He has received contributions to his resarch fund but does not accept personal remuneration from companies.

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