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New drugs for prostate cancer

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OBJECTIVE

- To describe some of the most exciting late stage clinical developments in the field of new therapies for advanced prostate cancer.

METHODS

- Pubmed was searched for articles pertaining to prostate cancer therapeutics clinical trials in the last 3 years.

RESULTS

- Key positive trials in the areas of androgen resistance, tumour immunology, molecularly targeted agents and cytotoxics were reviewed and discussed in the context of metastatic prostate cancer.

CONCLUSION

- Treatments emerging from these areas of scientific endeavour are progressing into clinical trials and are both good cause for hope in patients, and excellent examples of mechanism based drug discovery.

What's known on the subject? and What does the study add?
Recent studies have demonstrated the efficacy of various new treatments. These have been in diverse areas of therapeutics research, including immunology and targeted biological therapy, as well as in new ways of approaching hormone refractory disease. The present paper seeks to review all of the key advances that have been reported in late-stage clinical studies and place them into the context of managing patients with advanced prostate cancer.

KEYWORDS

prostate cancer, clinical trials, new treatments

INTRODUCTION

The last 3 years have seen more progress in the field of experimental therapeutics for advanced prostate cancer than has been seen in the last three decades. New therapeutic agents have been developed that exploit advances in our knowledge of prostate cancer cell biology, chemoresistance, tumour immunology and androgen regulation. Treatments emerging from these areas of scientific endeavour are progressing into clinical trials and are both good cause for hope in patients, and excellent examples of mechanism-based drug discovery. In the present review we describe some of the most exciting late-stage clinical developments in the field of new therapies for advanced prostate cancer.

NEW HORMONAL TREATMENTS THAT OVERCOME ANDROGEN RESISTANCE

The hormonal treatment of prostate cancer has, like the disease itself, a very long natural history. Orchiectomy for prostate conditions was first described in 1893 by W. H. White (cited in [1]), but not brought to the attention of clinicians until the 1940s when Huggins and Hodges [2] established the efficacy of oestrogens and orchiectomy as treatments for prostate cancer. These were the standards of care until the early 1980s when the LHRH agonists entered clinical practice. These agents, in combination with an anti-androgen, have eventually become the 'gold standard' for treatment of advanced prostate cancer [3–5]. In the early 1990s anti-androgen withdrawal responses were described [6] and chemotherapy was found to have a palliative role [7]. In the 1990s chemotherapy was shown to have a survival role [8]. In this current decade we have entered an amazing time for drug discovery where a host of new agents are in trial.

The trouble with prostate cancer is that ultimately, regardless of our very best endeavours, resistance to treatments emerges and therapies become ineffective. Clinical and biochemical progression of the cancer is seen despite maximum androgen blockade, chemotherapy and a cascade of sequential hormonal manipulations, so that for patients with metastatic disease the 5-year survival rate is ≈25% [5]. Death from prostate cancer clearly remains the greatest of the clinical problems that face patients with prostate cancer, and the biggest challenge that faces clinical scientists.

EXPLOITING THE MECHANISMS FOR HORMONAL RESISTANCE

So what do we understand about the biochemical basis for the emergence of hormonal resistance? Many pathways are responsible. Firstly, it is clear that both mutations and amplification of the androgen receptor that facilitate signalling in low testosterone environments occur as part of clonal selection [9]. There are also changes in cellular enzymatic pathways that bypass dependence on extragonadal sex steroid synthesis. Thus, splice variants of the androgen receptor can continue to signal without a functional ligand-binding site [10,11], and both intra-tumoural [12] and adrenal [13] sex steroid production becomes important in what has been traditionally

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labelled as hormone refractory disease. Furthermore, increases in levels of androgen receptor (AR)-binding cofactors and adaptor proteins can facilitate AR binding of androgen response elements in DNA in prostate cancer, providing ongoing pro-growth signalling in castrate conditions. One such mechanism is the interaction between AR and adaptor proteins such as CRKL that can rescue AR activity using an alternative growth factor signalling pathway, even in the presence of androgen blockade with bicalutamide [14].

The term hormone 'refractory' prostate cancer (HRPC) is therefore inaccurate as a continued dependence on signalling involving the androgen receptor is indeed present and necessary in prostate cancer that is progressing, despite castrate serum levels of testosterone. This has implications for new drug development as there is much evidence to suggest that the androgen signalling pathway remains the key player in metastatic prostate cancer. As such, it remains a key target.

An understanding of these mechanisms points to ways in which new treatments can be developed. One strategy has been to try and block adrenal and intra-tumoural androgen production based on an understanding of steroid synthetic pathways. Ketoconazole is a non-selective inhibitor of adrenal androgen synthesis and lowers testosterone and dehydroepiandosterone (DHEA) levels through inhibition of multiple enzyme pathways including P45014DM and CYP17. When used in the castrate-resistant setting, PSA responses are observed in 20–60% of patients and responses are generally durable for 3–7 months; however, at the dose of 400 mg three times daily significant incidences of grade 3–4 toxicities are seen, and this can limit clinical use [15].

The observation of the over expression of CYP17 in prostate cancer tumours [16] has led to the synthesis of abiraterone, a selective steroid biosynthesis inhibitor which decreases circulating testosterone to undetectable levels in patients with already castrate serum levels. In a phase II study on 33 chemotherapy-naïve men with HRPC a >50% PSA reduction was seen in 85% of the men [17]. In a further study of docetaxel pre-treated men, remarkably, ≈50% had a >50% response in PSA level. This is clearly extremely promising in a pre-treated population with no current treatment options. The phase III trial in the post-docetaxel setting has shown a significant improvement in overall survival across all subgroups vs placebo (median 14.8 months) [18]. It is interesting to note that this dramatic activity is present in chemotherapy-naïve patients, and a phase III trial has recently finished accrual that will examine the drug's effect in this group. It is anticipated, however, that abiraterone could be even more effective in this setting. A second novel and selective CYP17 inihibitor, TAK-700, is also in phase II clinical studies having shown safety and efficacy in an open-label phase I study last year [19].

The androgen receptor is a transcription factor that is a member of a supergene family of cellular receptor proteins that include the vitamin D and oestrogen receptors. The androgen receptor, after combination with androgens, associates with cofactors, translocates to the nucleus, binds with DNA and initiates a series of events that include transcription and cell division. Anti-androgens interfere with this process, competing with androgenic steroids for their binding sites on the androgen receptor and limiting transcriptional activity. Internalization of the androgen receptor is key to its function in the nucleus as a transcription factor. A new agent, MDV3100, specifically blocks this cytosolic translocation and DNA binding. Encouragingly, in phase I–II studies, anti-tumour effects were seen at every dose level with 56% of patients with HRPC obtaining a >50% decrease in PSA with a similar decrease in circulating tumour cells [20]. The phase III 'AFFIRM' study has completed accrual in 2010 and the results are eagerly anticipated.

CYTOTOXIC CHEMOTHERAPY: THE LANDSCAPE AFTER DOCETAXEL

In 2004, two landmark studies showed the efficacy in HRPC of the taxane drug docetaxel in combination with prednisolone. An overall survival benefit of ≈2.9 months and a PSA response of >50% were seen in almost 50% of patients [8] compared with another chemotherapy drug, mitroxantrone.

In March 2010 the activity of a new taxane, carbazitaxel, for use in docetaxel-treated patients with HRPC was announced. Data was presented of the effects of carbazitaxel as shown in the phase III 'TROPIC' study. Eleven weeks after the presentation the US Food and Drug Administration (FDA) approved carbazitaxel as a treatment for prostate cancer, a state of laudable regulatory activity that we would hope might be reproduced in the UK.

Carbazitaxel was evaluated in patients with prostate cancer because of its decreased affinity for the multidrug resistance protein-P (or MDR-P) cellular efflux pump compared with other taxanes. This large multicentre study showed an overall survival benefit of ≈3 months in comparison with mitroxantrone [21,22].

Satraplatin is a third generation oral platinum-based cytotoxic chemotherapy agent. A recent phase III study ('SPARC') in patients with HRPC who had already been treated with one previous chemotherapy agent showed a 33% decrease in time to progression, but overall survival did not significantly differ in the two study arms, much to the chagrin of the company organizing the study. Many of us in oncology feel that satraplatin may well have activity which could have been demonstrated if satraplatin had been given as a first line rather than a second line agent, particularly as significant benefits in levels of pain and PSA values were seen in a group of patients with 'end-stage disease' [23].

It is clear, however, that cytotoxic chemotherapy has its limitations, and although the cell kill that is offered is theoretically desirable in any anti-cancer therapy, the considerable side effects inherent in these non-targeted drugs remain a major practical problem. Other ways of achieving control of prostate cancer have therefore been explored.

IMMUNOTHERAPY

Traditionally immunotherapy has been focused on tumours such as RCC and malignant melanoma that would seem to have a greater dependence on the host immune system dysregulation than many other cancers. These views as to the importance of the immune system in the control of these cancers have derived form the observations of spontaneous regression of metastases [24] and the effects of

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TABLE 1 Targeted agents in recent clinical trials

Target	Agent	Phase	Summary	ID
PI3K/mTOR	Everolimus	II	First and second line metastatic HRPC	NCT00459186
	Deforolimus	II		NCT00110188
VEGF	Bevacizumab	III	Doc+ Bev as first line HRPC	NCT00110214
VEGF receptor	Sorafenib	II	With Doc +/– as first line metastatic HROC	NCT00589420
	Sunitinib	II		NCT00137436
		III		NCT00676650
VEGF trap	Aflibercept	III	With Doc +/– for first line metastatic HRPC	NCT00519285
PDGFR	Imatinib	II	With Doc +/– for first line metastatic HRPC	NCT00080678
EGFR	Gefitinib	II	+ Everolimus for first line metastatic HRPC	NCT00085566
BCl-2	Oblimersen	II	With Doc +/– for first line metastatic HRPC	NCT00085228
IGF-1R	IMC- A12	II	Mitroxantrone +/– IMC for second line HRPC	NCT00683475
Endothelin-1	Atrasentan	III	Doc +/– Atra for first line metastatic HRPC	NCT00134056
RANK ligand	Denosumab	III	Vs. bisphosphonate in metastatic HRPC	NCT00321620
Vitamin D	Calcitriol	III	+/– Doc in first line HRPC	NCT00273338
CYP17	Abiraterone	III	Vs placebo in first and second line metastatic HRPC	NCT00887198
				NCT00638960
Androgen receptor	MDV3100	III	Vs placebo in metastatic HRPC	NCT00510718
BCR/ABL	Dasitinib	III	With Doc in first line metastatic HRPC	NCT00439270
CTLA4	Ipalimumab	III	Vs placebo in second line metastatic HRPC	NCT00861614

Doc, docetaxel; NCT, clinical trials registration number (http://www.clincaltrials.gov).

immunotherapy [25]. In patients with prostate cancer there is much less strong evidence of the importance of the immune system in the control of the disease, but efforts have been made in the pre-clinical setting to try and manipulate the immune system to elicit host immune reactions to prostate cancer cells. In this context, granulocyte macrophage–colony stimulating factor (GM-CSF)-secreting cancer vaccines have been used as a therapeutic strategy. These efforts are based on the hypothesis that a defective class I MHC on the cell surface is partly responsible for the low immunogenicity of prostate cancer. Because GM–CSF is a potent stimulator of dendritic cells, which are key in antigen uptake and expression, it was postulated that a vaccination programme could reverse this defect [26].

The GVAX prostate cancer vaccine was developed using GM-CSF-expressing prostate cancer (LNCaP) cells. Clinical and immunological responses with limited toxicity had been seen in the phase II setting; however, phase III studies (VITAL-1 and -2) failed to show a survival benefit. These negative results contrast with another vaccine study based on a poxvirus vector using a prostate antigen and co-stimulatory molecules. The phase II 'PROSTVAC-VF' study has failed to meet its primary endpoint which was an increase in progression-free survival; the results of a phase III study are awaited [27].

Another key development is in the area of adoptive immunotherapy. In this technique, autologous peripheral blood mononuclear cells are presented to recombinant prostate cancer antigens *ex vivo* and then re-introduced to the patient. Sipuleucel T (PROVENGE) is the first cancer vaccine to gain FDA approval for use, and is licensed in metastatic HRPC. The landmark phase III study of sipuleucel-T immunotherapy, published earlier this year, showed an overall survival benefit of ≈4.1 month [28] but with a surprisingly small tumour response rate. Despite its approval, obstacles to the widespread adoption of this treatment remain. Fundamentally the technology and equipment needed to provide an individualized adoptive immunotherapy service to a large population with such a common cancer are considerable [29].

TARGETED THERAPIES

As our understanding of the biological pathways involved in the propagation and survival of the prostate cancer cell have increased, the number of options available for specific drugs to target aberrant cellular machinery has increased concordantly. Some of these have been modelled on approaches that have been successful in other malignancies. These include the inhibition of specific SRC kinase motifs in key oncogenic proteins. Examples include sunitinib, which targets the vascular endothelial growth factor (VEGFR) and epidermal growth factor (EGFR) kinases in RCC, and traztuzumab which targets HER2 receptor in breast cancer. Table 1 shows targeted agents currently in clinical trials for prostate cancer.

The inherent attractiveness of these therapies in a clinical setting is that the majority of treatments target key oncoproteins responsible for one of the 'hallmarks' of cancer that separate normal prostate epithelial cells from frankly malignant cells, and as such would 'spare' healthy tissue. But how are prostate cancer cells different from 'normal' prostate cells? The existence of a prostate cancer 'stem cell' has not been proven, however, the characteristics of malignant cells have been defined. Malignant cells have at least six characteristics that include sustained

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angiogenesis, evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis and finally limitless replicative potential [30]. These capabilities are acquired in the form of genetic and epigenetic mutations and can be viewed as a multilevel complex circuit of protein, RNA and DNA interactions.

In gastrointestinal stromal tumours a gain of function mutation in C-KIT observed in >95% of tumours has provided a rational target for therapy [31]. Subsequently great success has been achieved clinically in inhibiting this tyrosine kinase with imatinib mesylate [32]. In prostate cancer, however, no common gain of function mutation has been identified in a tumour-specific oncoprotein. This fact, and the redundancy of many of the signalling cascades, may explain the lack of success so far in early clinical trials [33]. For example, although EGFR is overexpressed in 40–80% of prostate cancer cells there is no specific activating mutation [34]. In a phase II study of 51 patients with HRPC with the tyrosine kinase inhibitor Gefitinib, minimal activity was seen and only one PSA response was reported [35]. Similarly, high levels of platelet-derived growth factor (PDGFR) are seen in prostate cancer but single-agent activity with a PDGFR inhibitor has been disappointing [36]. Oblimersen is an antisense oligonucleotide that hybridizes to Bcl-2 mRNA. Bcl-2 is a key anti-apoptotic protein that is overexpressed in prostate cancer and confers resistance to a number of chemotherapy drugs including the taxanes. Despite promise in early phase work, a phase II study did not show a significant benefit in the oblimersen and docetaxel group when compared with docetaxel alone [37].

To overcome the challenge of redundancy in cellular pathways, rational combinations of targeted agents are being employed, e.g. the use of evirolimus with gefitinib to target the PI3K pathway downstream of EGFR (Table 1). However, for the reasons discussed above, without a key mutation to target it is difficult to see how this approach could be predicted to yield positive effects on outcome. Indeed many agents in the trials listed in Table 1 have now been reported on and have been negative, including avastin, oblimersen and calcitriol.

One potential problem in evaluating these new drugs is that of measuring outcome. Traditionally licensing has been granted after demonstration of overall survival benefit, generally with decreases in PSA and radiological measures of 'response' to a cytotoxic drug; however, as cytostasis rather than cytotoxicity is an expected outcome of some of the new biological agents, a response benefit is becoming more difficult to quantify, and may necessitate the use of sophisticated imaging or serum biomarkers [38].

The idea of using biomarkers as surrogates for outcomes in clinical trials is not new; indeed, serum PSA is measured routinely as a response marker. There have been many recent fascinating studies looking at cell cycle proliferation genes as prognostic, and in some cases predictive, biomarkers in prostate cancer. One study has recently examined a cohort of key genes in prostate tissue at diagnosis [39] and one in serum samples [40]. Serum microRNA profiles have also been used in this capacity [41]. Although these studies are excellent, the difficulty here is application. The ability to personalize treatments to a subset of patients who, in theory at least, may respond better to a certain intervention, at a certain time point in their disease is a major goal in oncology, but at the moment biomarkers are complicated and expensive, and for now experimental. In order for these to be adopted into routine practice, in trials or in the clinic they need to be validated against specific clinical questions in order to make them useful to the clinician.

INHIBITING BONE METASTASES

As prostate cancer has a predilection for metastasizing to bone, therapeutic strategies have emerged to target the signalling pathways involved. The receptor-activated NFkB ligand (RANK-ligand) has emerged as a key regulator in osteoclastic metastasis [42]. Antibodies against RANK ligand receptor-activated NFkb ligand in murine models of metastatic prostate cancer have increased survival [43]. Denosumab, one such monoclonal antibody, has been trialled against zoledronate to reduce skeletal events in metastatic HRPC in a phase III study involving 1900 patients. The results showed a significantly decreased rate of secondary skeletal events in the denosumab group, but with no difference in overall survival [44].

CLINICAL DECISIONS: WHAT ARE THE OPTIONS?

When presented with so many potential options for patients who have exhausted routine hormonal manipulations, what are going to be the determinants of the choice of treatments by clinicians and patients? Clearly the remit of the drugs licence and cost will have basic implications for socialized healthcare systems such as the NHS here in the UK. Regardless of this, the most obvious answer would seem to be that therapies will be tried in all suitable patients sequentially until progression or toxicity, as is the case currently, largely dictated by physician preference. With perhaps more than five drugs to choose from in HRPC, treatment may well become non-standard and complex.

As we are in the realm of more selective treatments there is an argument for attempting to sub-stratify patients. As discussed above, it may be that some biomarkers will enable clinicians to predict which patient will have the most to gain with a particular therapy, as has been elegantly demonstrated with the ALK-EML fusion mutation in non-small-cell lung cancer. As no such validated biomarker in prostate cancer exists, clinical trials addressing optimum sequencing, timing, and combinations of new drugs are urgently needed to guide clinicians. These will have to incorporate endpoints that are 'useable' to clinicians looking to know when to initiate and terminate the various treatment options.

CONCLUSION

The past 5 years have heralded a huge change in drug development for patients with prostate cancer. The most significant discoveries underpinning this change are in our understanding of the molecular mechanisms that define androgen or chemotherapy resistance in the 'hormone refractory' state. This knowledge of the cellular machinery and complex interactions has already produced many viable drug targets. As a result we have more treatments approved and licensed this year

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for advanced disease than in the previous 5 years combined. However, a note of caution remains: how do we afford and access ever more expensive treatments that are currently not curative but prolong life, in a society with increasingly limited resources? A great deal of hope for patients and their families rests on these exciting new agents that herald a new era in prostate cancer treatment and, by equal measure, a great deal of trepidation awaits clinicians for the difficult conversations that must lie ahead.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **AR**, androgen receptor; **GM-CSF**, granulocyte macrophage-colony stimulating factor; **HRPC**, hormone refractory prostate cancer; **VEGF**, vascular endothelial growth factor; **EGFR**, epidermal growth factor; **PDGFR**, platelet-derived growth factor.

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