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Improving Hormone Therapy For Prostate Cancer

Prostate cancer is one of the most common cancers in men, with 1 in 8 men in the UK estimated to develop the disease at some point in their lives. However, thanks to better detection methods and treatment options, 10-year survival rates have tripled to almost 85% over the past 40 years, illustrating that prostate cancer can often be successfully treated [1]. Nevertheless, there remain some significant challenges to overcome. Diagnosis still relies heavily on detection of serum Prostate Specific Antigen (PSA) levels, but this test is neither sensitive nor specific enough, leading to false negatives and false positives. Moreover, PSA testing still cannot accurately differentiate between a tumour which is benign and one which is potentially metastatic, meaning some men get unnecessarily treated [2]. Grading and staging through biopsy examination will help determine the course of treatment, which may include surgery, radiotherapy, hormonal therapy and chemotherapy, or a strategic combination of the above. However, prostate cancer is widely variable to therapy, in that two apparently similar cases may respond very differently to the same regimen. So although the disease is now more manageable than ever before, work is needed to improve methods of detection and customising treatment for each prostate cancer patient. In this short review, the challenges and opportunities for improving the hormone therapy in prostate cancer treatment are discussed.

Hormone Therapy for Prostate Cancer

When Dr Charles Huggins took up a new post at the University of Chicago in 1927, he had little interest in cancer biology, making him a most unlikely candidate to revolutionise prostate cancer therapy. However, when he discovered that prostate cells are dependent on testosterone for growth, he wondered if depriving prostate tumours of the hormone could be a way to treat the cancer. He subsequently demonstrated that surgical castration of dogs with prostate cancer could indeed slow tumour growth, an effect subsequently shown to work in human patients. He then progressed to show that injection of female hormones (estrogens) could cancel out the effect of testosterone [3]. 'Chemical castration', as he called it, could be used to

effectively suppress tumour growth in patients with prostate cancer, with minimal side-effects. It was a ground-breaking discovery that won him the Nobel Prize in 1966 and formed the basis for androgen deprivation therapy (ADT) [4].

Nowadays, several clinically available drugs are available for use in ADT and others are in development. For localised, early-stage prostate cancer, ADT generally involves suppressing testosterone production by interfering with the mechanisms which regulate its biosynthesis in the body. Luteinizing hormone-releasing hormone (LHRH) agonists or gonadotropin-releasing hormone₁ (GnRH) inhibitors stop the pituitary gland producing luteinizing hormone (LH) needed to stimulate testosterone production in the testes. LHRH agonists are often given in combination with an anti-androgen, a drug which competitively blocks testosterone from binding to the androgen receptor (AR), thereby inhibiting AR-dependent growth signalling. For locally advanced prostate cancer anti-androgens are generally the favoured option. Notably, ADT for localised and locally advanced prostate cancer can be used in combination with radiotherapy, as several clinical trials over the past 30 years have shown that this approach can delay tumour progression compared to radiotherapy alone [5].

However, although patients receiving ADT for early-stage disease initially respond to treatment, they typically relapse within 2 years to castrate-resistant prostate cancer (CRPC), as mechanisms of androgen independence emerge in the tumour cell population. Historically, this would have meant moving to chemotherapy, but two ADT agents have recently shown benefit in management of later-stage metastatic CRPC (mCRPC). Enzalutamide is a second-generation anti-androgen, whereas abiraterone inhibits CYP17A1, a key enzyme in the synthesis of testosterone. Results to date are encouraging and ongoing trials continue to track how these drugs can benefit patients with mCRPC [6] (Table 1). Thus, ADT continues to be the mainstay therapy for the management of prostate cancer at its various stages, and targeting AR axis signalling remains the focus for development of new ADT drugs [7].

Overcoming resistance to ADT

Nonetheless, the problem of developing ADT resistance and progression to mCRPC

Table 1. Prostate Cancer Trials open to recruitment in Northern Ireland (From NI Cancer Trials Centre December 2016)

Trial Name	Aim of Trial
Stampede	Systemic Therapy in Advancing or Metastatic Prostate cancer - Evaluation of Drug Efficacy
UKGPCS	UK Genetics Prostate Cancer Study
Radicals	Radiotherapy and Androgen Deprivation in Combination after Local Surgery. A Randomised Controlled Trial in Prostate Cancer
Rapper	Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy
PROMPTS	prospective randomised phase III study of observation versus screening MRI and pre-emptive treatment in castrate resistant prostate cancer patients with spinal metastasis
PROSPER	a multi-national, Phase III, randomised, double-blind, placebo-controlled, efficacy and safety study of Enzalutamide in patients with non-metastatic castration-resistant prostate cancer
TOPARP	a phase II trial of Olaparib in patients with advanced castration resistant prostate cancer
PACE	international randomised study of laparoscopic prostatectomy vs stereotactic body radiotherapy (SBRT) and conventionally fractionated radiotherapy vs SBRT for early stage organ-confined prostate cancer
CASPIR	calcifications as an alternative to surgically implanted fiducial markers for prostate image guided radiotherapy (CASPIR) : a prospective feasibility study
ADRRAD	neo-adjuvant Androgen Deprivation therapy, pelvic Radiotherapy and Radium-223 for new presentation T1-4 NO/1 M1B adenocarcinoma of prostate
LAPCD	Life After Prostate Cancer Diagnosis
SPORT High-Risk Trial	a randomised feasibility study evaluating Stereotactic Prostate Radio Therapy in high-risk localised prostate cancer with or without elective nodal irradiation

remains a major clinical obstacle to successful treatment of prostate cancer. Numerous cellular alterations including gene mutation, AR amplification, bypass pathways, ligand-independent activation and growth of cancer stem cells can all produce tumour cells that are no longer dependent on testosterone for growth and are more likely to develop into incurable disease. The driving forces underlying these changes remain elusive and the focus of much research.

In our laboratory at Ulster University (UU), research funded by Prostate Cancer UK is focused on how tumour hypoxia may exert a selective pressure that encourages the growth of cancer cells with increased metastatic potential. Low oxygen levels are a common feature of solid tumours and have been repeatedly linked to tumour progression in several cancers [8]. Using xenograft mouse models of prostate cancer, we found that an anti-androgen drug, bicalutamide, actually induces a profound hypoxia by collapsing the tumour vasculature, resulting in an upregulation of pro-survival genes by hypoxia-resistant cells within the tumour and increased metastatic potential [9,10]. This may help explain why patients relapse after initially successful response, making it necessary to consider treatment strategies that can target the resistant cells escaping hormone therapy.

One way of doing this is to investigate the combination of ADT with new drugs.

At UU, we have recently reported that a novel hypoxia-activated prodrug (HAP) improves the ability of bicalutamide to control growth of human prostate tumours in mice [10]. This data suggests that the HAP becomes activated to its cytotoxic form in the hypoxic conditions induced by bicalutamide treatment, and kills resistant cells that would otherwise survive the hormone treatment. This study corroborates similar experimental findings from other pre-clinical studies that emphasise that physiological and molecular changes taking place in individual tumours in response to treatment should receive careful consideration in developing therapeutic regimens. Our on-going and planned work now intends to demonstrate the potential of this new drug in combination with other ADT drugs, such as enzalutamide.

This is timely work as the idea of combinatorial drug treatment has gained considerable momentum in recent years. In particular, recent results from the CHARTED [11] and STAMPEDE [12] clinical trials have shown that use of docetaxel in combination with ADT improved relapse-free survival in patients with high-risk localised prostate cancer, proving that combining ADT with other types of drug can benefit prostate cancer sufferers. Similar on-going trials are investigating both the combination and the scheduling of different chemotherapeutic drugs (and/or radiation) with ADT on patient relapse

and overall survival (Table 1). However, improved ways of predicting which patients will respond to which drugs is needed. Making the right decisions on what drug to use, when to treat, who to treat and, importantly, who not to treat, require better knowledge about the mechanisms that drive prostate cancer progression in order to improve patient stratification in the clinic.

Personalised Medicine

The drive towards personalised medicine depends on the discovery of biomarkers that can allow molecular stratification of patients. Such information is likely to reside in the vast arrays of data detailing the specific genetic characteristics of individual prostate tumours gathered from genomic profiling in recent years. Comprehensive bioinformatics analyses of the data shows that a wide molecular diversity exists in human prostate tumours [13]. Such tumour heterogeneity may help explain why patients presenting with pathologically similar tumours can respond very differently to the same course of treatment. For example, primary prostate cancers are highly variable in AR activity, with increased AR-dependent signalling linked to gene mutations in SPOP and FOXA1 [13]. Knowing whether a tumour carries these mutations or not can help determine the most appropriate ADT approach for a patient and subsequent tracking of those gene mutations can

inform adaptive drug administration. Likewise, knowing the mutational status of the AR gene itself will be critical in predicting treatment outcome [7,13]. For instance, enzalutamide cannot bind to an abnormal splice variant of the AR called AR-V7; patients harbouring this mutation would be unlikely to respond to that particular drug, emphasising the need to stratify patients by molecular profiles. Indeed, AR-V7 can be detected in patient blood samples and efforts to validate this screening for clinical application are underway [14].

Non-invasive biomarkers that can be measured in biofluids are an attractive option for clinical use. We are encouraged by the potential of microRNAs as markers of prostate progression and treatment response. These small RNA molecules are

important regulators of cell function and many of them are aberrantly expressed in prostate cancer. Significantly, they are much more stably preserved than other RNA species in clinical samples, including fresh and fixed tissues, serum and urine, and can be readily detected using highly specific and sensitive PCR-based assays. Thus, both retrospective and prospective studies can determine the value of these as biomarkers of prostate cancer in different patient samples. Early evidence suggests that they can be used as circulating serum markers that predict treatment outcome [15]; our research effort is focused on identifying other microRNAs that have similar potential as serum-based biomarkers [16].

Conclusions

Improving ADT by developing precision medicine for individual patients is no small undertaking, but it is not an unrealistic proposition. Across the world, clinicians, researchers and industry are developing innovative ways to improve management of prostate cancer, and prostate cancer patients have more informed opportunities to participate in clinical trials. Treatment of prostate cancer continues to make huge strides since Charles Huggins' breakthrough work, but his words of wisdom remain as relevant as ever. "Discovery is our business," he once told his colleagues. "Make damn good discoveries." As a research community, we are aiming to make discoveries so good that few men need die from prostate cancer in future.

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