New perspectives on hormone therapy for prostate cancer

Dr Declan McKenna, Lecturer in the School of Biomedical Sciences at Ulster University, Coleraine, outlines past, present and future perspectives on hormone therapy for prostate cancer

When Dr Charles Huggins took up a new post at the University of Chicago in 1937, he had little interest in cancer biology. A physiologist by training, he was more interested in glandular secretions and was researching how prostatic fluid could control the growth of the prostate. His early animal experiments revealed that if the castrated dog’s prostate gland would shrink and the prostatic fluid would unsurprisingly dry up. However, when the operated dog was then injected with testosterone this response was prevented, demonstrating that the cells of the prostate gland depend on testosterone for growth. But then Huggins started to ask questions about what happens if dogs with prostate tumours were deprived of testosterone. Would the prostate tumour cells also depend on the hormone for growth? A series of experiments demonstrated that surgical castration of dogs with prostate cancer did indeed slow the tumour growth and this observation was subsequently shown to work in human patients as well. It was convincing evidence but Huggins, no doubt aware that removal of their testicles might not be the best therapeutic option for most men, took things a step further. Could testosterone action be blocked by adding the hormone antagonist to counter the male hormone?

Throughout the 1950s, Huggins embarked on a programme of research that defined the use of anti-androgens as a means to cure or control a variety of tumours. Androgens are produced by the male testes and play a key role in maintaining the male sex characteristics by stimulating the development of male reproductive organs. However, patients taking LH-RH agonists for the first time can experience a phenomenon known as a testosterone flare, as excess LH production is briefly stimulated prior to being blocked. For this reason, LH-RH agonists are often given in combination with an anti-androgen, which will block LH-induced testosterone from binding to the androgen receptors (AR), thereby inhibiting AR-dependent growth signal.

Consequently, releasing hormone (GnRH) antagonists also work to inhibit LH action but are less commonly used.

For locally advanced prostate cancer, anti-androgens are generally the preferred option. Important, 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.

However, although patients receiving ADT for early stage disease initially respond to treatment, they typically relapse within two years to cause resistant prostate cancer (CRPC), as mechanisms of androgen independence emerge in the tumour cell population. Historically, this meant switching treatment to chemotherapy, but in recent years two ADT agents have shown benefit in management of intermediate metastatic CRPC (mCRPC). Enzalutamide is a second-generation anti-androgen, while abiraterone inhibits CYP17A, a key enzyme in the synthesis of the testosterone.

Promising results to date and ongoing trials continue to track and compare the benefit of these drugs in advanced prostate cancer. Thus, ADT continues to be the mainstay therapy for management of prostate cancer at all stages of treatment and in combination with ADT improved relapse-free survival in patients with high-risk localized prostate cancer, proving that combining ADT with other drug types can improve prostate cancer outcomes.

Other ongoing trials are still investigating both the combination and the scheduling of different chemotherapeutic drugs (and/or therapy) for patients with metastatic CRPC, which are more likely to develop into inurable mCRPC. The driving forces underlying these changes remain elusive and are the focus of much research.

In our laboratory at Ulster University (UU), we are interested in how tumour hypoxia, an important feature of solid tumours, may exert a selective pressure which enhances the growth of cancer cells with increased metastatic potential. Using murine xenograft models of prostate cancer, we have shown that the androgenic antagonist alone actually induces a profound hypoxia response, potentially increasing the tumour vasculature, resulting in an up-regulation of pro-survival genes by hypoxia-resistant tumour cells on the distant macrophages that reside in these hypoxic tumour hypoxic cells that would otherwise survive the hypoxic tumour environment. Hypoxia-driven therapy aims to further demonstrate the potential of HIF inactivation by hypoxia-inducible factor (HIF) inhibitors by measuring the physiological and molecular changes taking place with the tumour in response to treatment.

Future perspectives

Although chemotherapy and radiation therapy have undoubtedly provided invaluable data to help improve the detection and treatment of prostate cancer, the tailored therapy will require new strategies to target and inhibit the proliferation of tumour cells that escape hormone therapy and this means identifying for any given patient whether administration of ADT should be immediately deferred, prolonged, adjusted, adjunctive, or combined. This idea of combinatorial drug treatment has gained traction in recent years, in particular, recent results from the CHARMED and STAMPEDE clinical trials have revealed that use of docetaxel (a taxane drug) in combination with ADT improved relapse-free survival in patients with high-risk localized prostate cancer, proving that combining ADT with other drug types can improve prostate cancer outcomes.

Another ongoing trial is still investigating both the combination and the scheduling of different chemotherapeutic drugs (and/or therapy) for patients with metastatic CRPC, which are more likely to develop into inurable mCRPC. The driving forces underlying these changes remain elusive and are the focus of much research. In our laboratory at Ulster University (UU), we are interested in how tumour hypoxia, an important feature of solid tumours, may exert a selective pressure which enhances the growth of cancer cells with increased metastatic potential. Using murine xenograft models of prostate cancer, we have shown that the androgenic antagonist alone actually induces a profound hypoxia response, potentially increasing the tumour vasculature, resulting in an up-regulation of pro-survival genes by hypoxia-resistant tumour cells on the distant macrophages that reside in these hypoxic tumour hypoxic cells that would otherwise survive the hypoxic tumour environment. Hypoxia-driven therapy aims to further demonstrate the potential of HIF inactivation by hypoxia-inducible factor (HIF) inhibitors by measuring the physiological and molecular changes taking place with the tumour in response to treatment.

Advances in genomic technology and increased use of new therapeutics mean that vast arrays of data detailing the genetic complexity of individual prostate tumours have been gathered. Comprehensive bioinformatics analyses of this data reveal a wide heterogeneity and molecular diversity in prostate tumours, which helps explain why patients can respond or progress with pathologically similar tumours can have very different responses to the same treatment.

The key to improved patient stratification in the clinic, therefore, lies in both understanding the different subtypes of prostate cancer that exist and determining which treatments sub these sub-types will best respond to. For example, primary prostate cancers exhibit a wide variability in AR activity, with AR-dependent signalling linked to gene mutations in SPINK1 and FOXA1. Knowing whether a tumour carries these mutations or not can help determine the most likely androgen receptor pathway for a patient, and subsequent testing of their tumour for expression of AR mutations can help guide treatment.

In this regard, understanding the mutational status of AR itself will be unlikely to respond to that particular drug, further emphasizing the need to stratify patients prior to treatment research. In this regard, recent research has shown that AR-V7 can be detected in a small blood sample and efforts to validate this screen for clinical application are currently ongoing.

Similarly, in our lab, we are excited about the potential of microRNA as modifiers of disease progression. These small RNA molecules are much more stably preserved in blood than any other tissue and can be readily detected in tissue, serum and urine specimens. Using our laboratory’s expertise and developing novel diagnostic and therapeutic strategies to take advantage of the physiological and molecular changes taking place with the tumour in response to treatment.

Developing precision medicine for individual patients is no small undertaking, but it is an achievable goal. Clinicians, researchers, industry and health professionals worldwide are all working continually to develop innovative approaches for the detection and treatment of prostate cancer. While, while patients themselves are often more informed about participation in clinical trials and available treatments.

Treatment of prostate cancer has made huge strides since Dr Charles Huggins broke through work, but his words are still as relevant as ever. “I’m going to believe,” he once told his colleagues. “Make damn good discoveries.” As a research community, we are aiming to make discoveries so good, they will mean no one need die of prostate cancer.

References on request.

Dr Declan McKenna is a Lecturer in the School of Biomedical Sciences at Ulster University, Coleraine. His research is focused on understanding the mechanisms of prostate cancer progression and the potential for developing imaging for diagnosis, prognostic and potential therapeutic interventions in prostate cancer. Contact: Dr Declan McKenna, Lecturer in Medicinal and Molecular Sciences, School of Biomedical Sciences | University of Ulster | Coleraine | BT52 1SA | e-rick.mca@ulster.ac.uk | www.ulster.ac.uk

Table 1: Selection of ADT drugs currently used for treatment of prostate cancer

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH-RH agonists</td>
<td>degarelix</td>
<td>Zoladek 300, Norgestrol 600</td>
</tr>
<tr>
<td>Androgens</td>
<td>bicalutamide</td>
<td>Casodex</td>
</tr>
<tr>
<td>CYP17A inhibitor</td>
<td>abiraterone</td>
<td>Zytiga</td>
</tr>
<tr>
<td>Geronton</td>
<td>nilutamide</td>
<td>Nilutine</td>
</tr>
</tbody>
</table>

Androgen deprivation therapy (ADT) is all available options for initial treatment and five-year survival rates are approximately 50% overall, demonstrating that prostate cancer can often be successfully treated.

On day 1, ADT blocks several drugs that can effectively treat prostate cancer (Table 1), while others are in development. For locally advanced, early-stage prostate cancer, ADT generally involves suppressing testosterone production by interfering with the mechanisms that regulate its biosynthesis in the body. Luteinising hormone-releasing hormone (LH-RH) agonists stop the pituitary gland producing luteinising hormone (LH), which is needed to stimulate testosterone production in the testes.

However, patients taking LH-RH agonists for the first time can experience a phenomenon known as a testosterone flare, as excess LH production is briefly stimulated prior to being blocked. For this reason, LH-RH agonists are often given in combination with an anti-androgen, which will block LH-induced testosterone from binding to the androgen receptors (AR), thereby inhibiting AR-dependent growth signal.

Cinaderolepine-releasing hormone (GnRH) antagonists also work to inhibit LH action but are less commonly used.

For locally advanced prostate cancer, anti-androgens are generally the favoured option. Importantly, 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.

However, although patients receiving ADT for early-stage disease initially respond to treatment, they typically relapse within two years to cause resistant prostate cancer (CRPC), as mechanisms of androgen independence emerge in the tumour cell population. Historically, this meant switching treatment to chemotherapy, but in recent years two ADT agents have shown benefit in management of intermediate metastatic CRPC (mCRPC). Enzalutamide is a second-generation anti-androgen, while abiraterone inhibits CYP17A, a key enzyme in the synthesis of the testosterone.

Promising results to date and ongoing trials continue to track and compare the benefit of these drugs in advanced prostate cancer.

Table 1: Selection of ADT drugs currently used for treatment of prostate cancer

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH-RH agonists</td>
<td>degarelix</td>
<td>Zoladek 300, Norgestrol 600</td>
</tr>
<tr>
<td>Androgens</td>
<td>bicalutamide</td>
<td>Casodex</td>
</tr>
<tr>
<td>CYP17A inhibitor</td>
<td>abiraterone</td>
<td>Zytiga</td>
</tr>
<tr>
<td>Geronton</td>
<td>nilutamide</td>
<td>Nilutine</td>
</tr>
</tbody>
</table>