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Authors

Zoubeidi, Amina

Ghosh, Paramita M

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THEMATIC REVIEW

Celebrating the 80th anniversary of hormone ablation for prostate cancer

Amina Zoubeidi[1] and **Paramita M Ghosh**[2,3,4]

[1]Department of Urologic Sciences, University of British Columbia, Vancouver, British Columbia, Canada
[2]Department of Urologic Surgery, School of Medicine, University of California Davis, Sacramento, California, USA
[3]Department of Biochemistry and Molecular Medicine, School of Medicine, University of California Davis, Sacramento, California, USA
[4]Department of Veterans Affairs, Northern California Health Care System, Mather, California, USA

Correspondence should be addressed to A Zoubeidi: azoubeidi@prostatecentre.com

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Abstract

In this issue of *Endocrine-Related Cancer*, we are celebrating the 80th anniversary of hormone ablation as treatment for metastatic prostate cancer. Our understanding has evolved from the observation that androgen withdrawal, either surgical or pharmacological, resulted in prostatic atrophy in animal models, to its application in patients, to investigation of the mysterious way in which prostate cancer escapes androgen dependence. We are now in an era of novel AR pathway inhibitors, the combination of androgen ablation with chemotherapy, PARP inhibitors, immunotherapies, guided radiotherapy, and novel drug application based upon genetic testing of individual tumors. In this special issue, we bring together a collection of eight reviews that cover not only the history of 80 years of progress after the initial identification of androgen ablation as an effective treatment of prostate cancer, but subsequent improvements in the understanding of the biology of the disease, development of novel treatment paradigms, resistance to those treatments and disease progression following that resistance.

Key Words

- prostate
- androgen
- androgen receptor
- endocrine therapy

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Introduction

Localized prostate cancer can be treated with surgery; however, metastasized prostate cancer is usually treated with hormonal ablation. Improved diagnostic tools and earlier diagnosis has helped increase the 10-year survival of prostate cancer patients (Helgesen *et al.* 1996). By 1998, the 10-year relative survival for patients diagnosed with local and regional disease improved to 95% (Brawley 2012), and is near 100% today. Five-year survival for distant-stage prostate cancer improved to 32.3% by 2016 and remains at that level today (Siegel *et al.* 2020).

In this special issue of *Endocrine-Related Cancer*, we are celebrating the 80th anniversary of hormone ablation as a treatment for metastatic prostate cancer. Our understanding has evolved from the observation that androgen withdrawal, either surgical or pharmacological, resulted in prostatic atrophy in animal models, to its application in patients, to the investigation of the mysterious way in which prostate cancer escapes androgen dependence. We are now in an era of novel AR pathway inhibitors, the combination

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of androgen ablation with chemotherapy, PARP inhibitors, immunotherapies, guided radiotherapy, and novel drug application based upon genetic testing of individual tumors (Fig. 1). In this Anniversary Issue, we bring together a collection of eight reviews that cover not only the history of 80 years of progress after the initial identification of androgen ablation as an effective treatment of prostate cancer, but subsequent improvements in the understanding of the biology of the disease, development of novel treatment paradigms, resistance to those treatments and disease progression following that resistance.

History

In an article in this special issue, 'Targeting androgen receptor signaling: a historical perspective', Davies & Zoubeidi (2021) outline the history of prostate cancer treatment using androgen ablation. An 18th century observation laid the foundation for the most important discovery of the 20th century in prostate cancer. The concept of androgen ablation was discussed as early as 1786 when John Hunter demonstrated that castration prevents prostate development in young bulls while inducing atrophy in adults (Hunter 1837). It was not until 1941 that Charles Huggins and Clarence Hodge performed the first castration surgically or by estrogen administration in eight patients with metastatic prostate cancer (Huggins *et al.* 1941). They observed that castration resulted in a decrease of serum acid-phosphatase and subsequently an increase in patient quality of life.

Targeting adrenal androgen production

In early 1960s, multiple clinical trials provided evidence that androgen ablation was merely palliative and not sufficient to cure prostate cancer, as Huggins noted that regression of the neoplasm is not complete (Huggins *et al.* 1941). Facing this challenge, new approaches of hormone manipulation were developed between 1960s and 1980s to block adrenal androgen production or androgen interaction to androgen receptor (Pavone-Macaluso *et al.* 1986, 1997, Trachtenberg *et al.* 2002). This was possible with the discovery of the structure of the hypothalamic hormone known as luteinizing hormone (LH)-releasing hormone (LHRH), which was shown to induce the pituitary to produce LH. LH binds to its receptor on the testes and activates testosterone production (outlined in Messner *et al.* 2020). Schally and Guillemin investigated ways to manipulate the hypothalamic–pituitary–gonadal axis and developed the first synthetic peptide agonists of LHRH (Tolis *et al.* 1982). Similarly, the antifungal ketoconazole (non-specific inhibitor of several cytochrome enzymes, involved in steroidogenesis including CYP17) accomplished PSA responses in some patients (Small *et al.* 1997, Kruit *et al.* 2004, Peer *et al.* 2014), but did not improve overall survival. This was traced to the fact that resistance to the treatment was observed in the majority of the patients.

Targeting the androgen receptor

The discovery of androgen receptor (AR) in late 1960s (Anderson & Liao 1968, Bruchovsky & Wilson 1968, Mainwaring 1969) revolutionized how we treat prostate

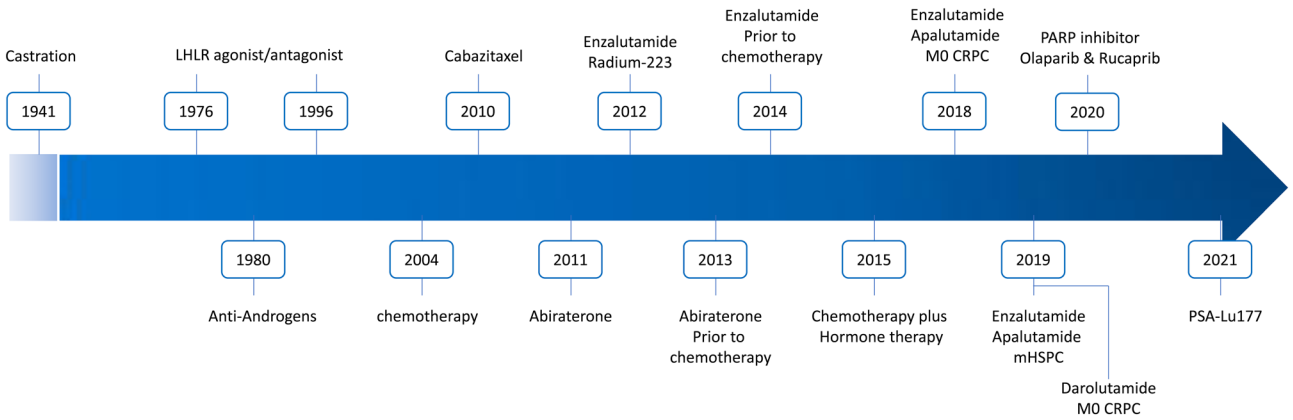

Figure 1
Treatment evolution of metastatic prostate cancer.

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cancer today. The first AR antagonist targeting the AR ligand binding domain (LBD) proved to be as effective as castration (Pavone-Macaluso *et al.* 1986) and was approved by the US Federal Drug Administration (FDA) in late 1980s, which was followed by the development of non-steroidal anti-androgens, such as flutamide in 1989 and biclutamide in 1995, as treatment for prostate cancer (Wirth *et al.* 2007). Similar to castration, LHRH agonist/antagonist or AR inhibitors as monotherapy were shown to be ineffective, which shaped the path for combination therapy (Labrie *et al.* 1982, Lefebvre *et al.* 1982). Meta-analysis from 27 phase III clinical trials concluded that combined androgen blockade improved 5-year survival by about 5% (Caubet *et al.* 1997, Bennett *et al.* 1999, Schmitt *et al.* 2001, Klotz 2008, Mitsiades *et al.* 2011); however, it invariably led to the development of castrate-resistant prostate cancer (CRPC) (Sayyid *et al.* 2017).

Reviving old concepts with potent inhibitors

In 'Androgen receptor signaling inhibitors: post-chemotherapy, pre-chemotherapy and now in castration-sensitive prostate cancer', Mitsiades & Kaochar (2021) ask 'Can a more comprehensive approach targeting all sources of androgenic stimulation delay emergence of resistance to ADT?' The development of CRPC was proposed to be caused by the low potency of AR antagonists and most likely prone to 'antagonist-to-agonist' conversion which was noticed in 15–30% CRPC treated patients (Kelly & Scher 1993, Leone *et al.* 2018). This phenomenon was also attributed to dysregulation of the AR complex via somatic-acquired events, including AR LBD gain-of-function mutations, AR amplification, overexpression, altered recruitment of steroid receptor coactivators (Culig *et al.* 1999, Chen *et al.* 2004, 2009, Leone *et al.* 2018) as well as *de novo* synthesis of androgen via cholesterol metabolism (Locke *et al.* 2008, Cai *et al.* 2011). CYP17A1, a member of the cytochrome P450 enzyme family, promotes the synthesis of steroid hormones including testosterone and dehydroepiandrosterone (DHEA), both precursors of the strong AR ligand dihydrotestosterone (DHT) (outlined in Messner *et al.* 2020). These findings provided the rationale for drug discovery screens to identify novel anti-androgens and novel CYP17 inhibitors with better pharmacodynamics and more durable responses.

Despite the fact that ketoconazole itself did not show a survival benefit, it did serve as a forerunner of CYP17 inhibitors. Abiraterone acetate (Abi) was developed as a more effective inhibitor of CYP17 with significantly higher potency and selectivity than ketoconazole (Barrie *et al.* 1994, Potter *et al.* 1995, Rowlands *et al.* 1995, Haidar *et al.* 2003). The first phase I study for Abi enrolled 21 men with chemotherapy-naïve CRPC and found that Abi-treated patients experienced significant tumor shrinkage and dramatic falls in prostate-specific antigen (PSA) levels (Attard *et al.* 2008). In 2010, the pivotal phase III COU-AA-301 trial showed survival benefit and was approved in 2011 (de Bono *et al.* 2011).

Since CRPC was still driven by AR, second-generation AR LBD inhibitors were developed, including enzalutamide, apalutamide and darolutamide. Enzalutamide was initially tested in men with metastatic CRPC previously treated with docetaxel-based chemotherapy in the phase III AFFIRM trial, showed positive survival benefits (Scher *et al.* 2012) and was approved by the FDA in 2012 for late-stage CRPC. Additional successful phase III clinical trials on enzalutamide were conducted including PREVAIL in men with asymptomatic metastatic CRPC without prior chemotherapy (Beer *et al.* 2014), and the ARCHES trial on men with high risk of metastatic progression or death in the castration-sensitive (CSPC) setting (Armstrong *et al.* 2019). It was later expanded to the setting of non-metastatic CRPC (nmCRPC) in 2018 (Sternberg *et al.* 2020) and metastatic CSPC in 2019 (Davis *et al.* 2019). In addition, other AR inhibitors apalutamide and darolutamide which have improved safety profiles compared to enzalutamide, have also been approved for non-metastatic CRPC (Fizazi *et al.* 2019, 2020) or for metastatic CSPC (Chi *et al.* 2019).

Following clinical integration of second-line hormone therapy, growing evidence shows that CRPC patients are progressing on CYP17 and AR inhibitors even when they were administered sequentially (Loriot *et al.* 2013, Noonan *et al.* 2013, Bianchini *et al.* 2014, Azad *et al.* 2015, Attard *et al.* 2018, de Bono *et al.* 2018, Khalaf *et al.* 2019). Cross-resistance between these two classes of AR pathway inhibitors (ARPI) is not surprising, as several mechanisms can provide resistance to both CYP17 inhibitors and second generation anti-AR including constitutively active AR variants (including ARv7).

Hormonotherapy and the bone microenvironment

In 'Second-generation hormonotherapy in prostate cancer and bone microenvironment', Bouleftour *et al.* (2021) discuss the effect of androgen ablation and second-generation anti-androgens on the bone. Proper functioning of the AR is essential both for bone development and for

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bone mass maintenance (Bellido *et al.* 1995, Kawano *et al.* 2003, Chen *et al.* 2019). As a result, androgen ablation is significantly associated with bone loss and increased risk of bone fractures (Abu *et al.* 1997, Notelovitz 2002). In addition, most prostate cancer patients weare older, and naturally undergo age-related decline in hormonal levels and are highly prone to bone loss (Manolagas *et al.* 2013). The receptor activator of NF-κB ligand (*RANKL*) gene, which encodes a major osteoclastogenesis inducer, was found to be a major regulator of bone density regulated by androgens (Kawano *et al.* 2003). Denosumab, a fully human MAB against RANKL, is used to improve bone mineral density and fractures in men receiving androgen-deprivation therapy for non-metastatic prostate cancer (Smith *et al.* 2009). Despite this, prostate cancer patients, especially those who are older, suffer significantly from bone loss and related side effects. Bouleftour *et al.* (2021) argue that currently, specific recommendations for bone health management in prostate cancer patients are lacking, and prospective studies assessing bone mineral density in patients treated with second-generation hormone therapy has not been conducted. It may be hoped that the collection of information provided in this issue would pave the way for such a study.

Emergence of aggressive variant prostate cancer

Two articles in this special issue, 'The heterogeneity of prostate cancers lacking AR activity will require diverse treatment approaches' by Labrecque *et al.* (2021) and 'Therapy considerations in neuroendocrine prostate cancer: what next?' by Beltran & Demichelis (2021) describe the advent of aggressive variant prostate cancers. Labrecque *et al.* describes AR indifferent and AR inactive prostate cancer and identify the role of SOX2, nBAF and LSD1 in the development of neuroendocrine prostate cancer. Beltran and Demichelis focus mainly on therapeutic aspects of neuroendocrine prostate cancer and identify numerous biomarkers that can predict its outcome.

With drugs targeting the AR pathway used in earlier disease settings, patients are living longer with longer exposure to systemic therapies. However, systemic therapies are not curative, and the treatment-resistant state remains a major medical problem. With the integration of potent ARPI, the archetypal course of prostate cancer was altered by the emergence of aggressive variants of prostate cancer with activated lineage programs. This includes *amphicrine* (expresses AR activity and neuroendocrine (NE) markers, retains luminal differentiation programs); *AR-low* (expresses low AR, high level of PSA and lacks NE markers); *double-negative prostate cancer* (DNPC: lacks AR expression and activity and lacks NE markers) (Labrecque *et al.* 2019) and the treatment-induced *neuroendocrine prostate cancer* (NEPC: loss of AR signaling, expresses neuroendocrine markers) (Beltran *et al.* 2011, 2016). The complexity surrounding the transition from an AR-dependent to an AR-indifferent phenotype has made it difficult to define histological or molecular features that consistently associate with the emerging CRPC phenotypes. Currently, no morphological characteristics have been described in clinical specimens to delineate an AR-active from an AR-inactive phenotype in AR-expressing CRPC. Furthermore, it is not yet clear that morphological features associate with the full spectrum of molecular phenotypes of NEPC (Beltran *et al.* 2011, 2016, Aggarwal *et al.* 2018, Labrecque *et al.* 2019). With exception of loss of PTEN, RB1 and TP53, genomic analyses have not clarified genomic features that reliably distinguish these phenotypes or that can be used to predict risk of conversion to AR-null or NE-positive states. Epigenetic alterations, including changes in DNA methylation, chromatin accessibility, SWI/SNF, and histone markers are distinguishing features of NEPC, suggesting a key role of epigenetics in driving prostate cancer adenocarcinoma to NEPC (Dardenne *et al.* 2016, Cyrta *et al.* 2020, Baca *et al.* 2021). Activation and coordination of lineage determining transcription factors (e.g. ASCL1, BRN2, ONECUT2, MYCN, FOXA1) (Lee *et al.* 2016, Bishop *et al.* 2017, Guo *et al.* 2019, Baca *et al.* 2021) and pluripotency factors (e.g. SOX2) (Bishop *et al.* 2017) and downregulation of REST (Zhang *et al.* 2015) appear to drive lineage programming. This lineage reprogramming may be mediated by an intermediary, de-differentiated 'stem like' state before cells differentiate toward a NE-like phenotype with loss of AR dependence. Patient with aggressive variants of prostate cancer is treated with systemic therapy regimen. The combination of cabazitaxel and carboplatin is now supported by NCCN guidelines as an option for patients with aggressive variant clinical features or unfavorable genomics (loss of function alterations involving at least two of PTEN, TP53, and RB1) (Suzuki *et al.* 2020).

Beyond hormone therapy DNA repair machinery targeting

While AR-dependent transcriptional activity is the main driver of prostate cancer progression, genomic instability is a major feature of prostate cancer. This phenomenon is described by Díaz-Mejía *et al.* (2021) in this special issue

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in the article entitled 'PARP inhibitors in prostate cancer: when to use them?'. This genomic instability is related to AR pathway and chronic inflammation leading to increased DNA damage (Godwin *et al.* 2013, Polkinghorn *et al.* 2013). These alterations in double-strand break repair genes will lead to impairment of error-free homologous recombination-mediated repair, favoring genomic instability and replicative stress. In prostate cancer, mutations of genes of the homologous recombination repair (HRR) and double strand break (DSB) pathways, mainly BRCA2, FANCA, RAD51 or PALB2; ATM, CHEK2 or CDK12, were observed 20–30% of patients with advanced prostate cancer (Abida *et al.* 2017, Chung *et al.* 2019). Some of these mutations arise in the germline DNA and are hereditary and were found in other cancers, including pancreatic, ovarian and breast cancer (Sokolova *et al.* 2020), suggesting patients with prostate cancer can benefit from genetic testing and selected therapy beyond ARPI using PARP inhibitors. Hence PARP inhibitors were tested in multiple clinical trials, including the PROFOUND study (de Bono *et al.* 2020). This trial was structured around two cohorts: cohort A included 245 patients with mutations in BRCA1, BRCA2 or ATM; cohort B included 142 patients with alterations in any of the 12 other prespecified genes (BRIP1, BARD1, CDK12, 363 CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L). The trial met the predefined threshold for overall survival and the PARP inhibitor olaparib was approved by FDA in 2020 for men with mCRPC and different DNA repair gene mutations offering a new treatment for these patients.

Immunotherapy

Although the effects of DNA repair defects and genetic/epigenetic aberrations on the cell division machinery are increasingly well-defined, it has become evident that the tumor microenvironment (TME), including stroma, endothelial and immune cells, plays an important role in prostate cancer disease progression and survival (Hinshaw & Shevde 2019). In this special issue, Kwon, Bryant and Parkes describe the role of immunotherapy in prostate cancer treatment in the article 'The tumor microenvironment and immune responses in prostate cancer' (Kwon *et al.* 2021). Large phase III clinical trials have failed to show improvement in overall survival with ipilimumab (a CTLA-4 inhibitor) (Kwon *et al.* 2014, Beer *et al.* 2017). However, these trials did demonstrate an acceptable toxicity profile, improved PFS with ipilimumab, and PSA response. Because of the limited benefit of monotherapy in the general setting, it was suggested that investigators select patients based on high genomic instability or mismatch repair efficiency that is known to increase neoantigen load with increased immune infiltration (Graham *et al.* 2020). Analysis of five clinical trials revealed that patients harboring genomic instability who received pembrolizumab reach objective response rate (Marcus *et al.* 2019). Because of the limited benefit of monotherapy, ongoing trials are investigating combination immunotherapy. For instance, the CheckMate trial evaluated ipilimumab and nivolumab for patients with mCRPC. Initial results have shown a response rate of 26% in the chemotherapy-naïve cohort and 10% in the group who failed taxane-based therapy (Sharma *et al.* 2020).

Radiation therapy

Throughout the advances in the last several decades, radiotherapy (RT) has remained a pillar of treatment in localized advanced disease. Importantly, the addition of hormone therapy to adjuvant RT resulted in a significant improvement in progression-free survival (Pilepich *et al.* 2005). Sandoval, Dohm and Yamoah, in this special issue, describe the role of radiotherapy, with or without immunotherapy in 'Management of early-stage metastatic prostate cancer: appraisal of locoregional treatments and radiation therapy, with or without immunomodulation' (Sandoval *et al.* 2021). Analysis of the RTOG 9408 study showed that the benefit of hormone therapy was seen mostly in intermediate-risk disease and was likely insufficient for men with high-risk disease (Jones *et al.* 2011). In a large retrospective analysis of over 1300 post-prostatectomy patients who were either placed under observation or given hormone therapy ± adjuvant RT showed significant increase in overall survival using androgen deprived therapy plus RT (Touijer *et al.* 2018). However, the HORRAD trial showed no difference in the overall survival in patient that received hormone therapy to those that received RT+hormone therapy (Boeve *et al.* 2019). Radium-223 is an alpha emitter that has been shown to target highly proliferative bone metastases (Bruland *et al.* 2006, Gomez-Veiga *et al.* 2018). Development of advanced assays and genomic risk stratification has increased the spectrum of using RT in prostate cancer. However, the use of RT in biochemical-recurrent disease was challenging because of the lack of sensitive modalities to detect positive nodes. Recently a very sensitive approach was developed based on the prostate-specific membrane antigen (PSMA) PET/CT imaging and become the recommended imaging

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modality in the setting of rising PSA (Gillessen *et al.* 2020). Interestingly, PSMA can be used beyond imaging not only for PET imaging but in the linking to the beta emitter lutetium-177, which has provided a novel approach to treat prostate cancer patients showing an average PSA decline in 75% of patients, which was supported by radiographic evidence of objective responses and stable disease (Yadav *et al.* 2019).

Current perspectives

Over 80 years, tremendous advances were achieved leading to changes in clinical practice. We built on observations from 19th and 20th centuries and developed potent AR pathway inhibitors, discovered and validated novel markers, established novel modalities for imaging and treatment and innovated on how to run clinical trials. We accepted that prostate cancer is not one disease. Today, we stratify patients and employ genetic testing. Yet, metastatic prostate cancer patients still die with treatment-resistant aggressive disease. We are advancing our understanding of mechanisms of treatment resistance, identifying targets and novel drugs. However, the only way we can save lives is to conduct clinical studies, which will be challenging, especially for rare phenotypes. We recommend embracing the concept of the STAMPEDE trial to tackle this problem. Briefly, STAMPEDE was initiated in 2005, and it is an ongoing multi-arm, multistage randomized clinical trial conducted in the United Kingdom and Switzerland testing various treatment in newly diagnosed or relapsing high risk, node-positive, or metastatic prostate cancer patients initiating long term hormone therapy. The unique trial design permits for test arms to be added over time and compared with contemporary standard of care single ongoing control arm. Overall, STAMPEDE has established docetaxel, abiraterone, and radiotherapy as new first-line treatment options. 4000 patients have experienced a survival benefit on the completed arms in STAMPEDE (James *et al.* 2017, Parker *et al.* 2018, Clarke *et al.* 2019, 2020). We hope that with this series of reviews in this issue of *Endocrine-Related Cancer*, future investigators will better understand the scope of the work needed to make such a trial easier to implement.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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