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Review article

Androgen receptor targeted therapies in metastatic castration-resistant prostate cancer – The urologists' perspective☆

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ABSTRACT

Androgen deprivation therapy (ADT), which involves the maximal suppression of circulating testosterone, underpins the treatment approach to metastatic hormone sensitive prostate cancer. Although initial responses are generally favourable, approximately half of cases progress to metastatic castrate resistant prostate cancer (mCRPC), rendering traditional hormonal therapies ineffective. mCRPC is defined by disease progression despite established ADT. New research has improved our understanding of the the molecular mechanisms behind metastatic castration-resistant prostate cancer (mCRPC). This has led to a renewed interest in the androgen receptor as a target for therapy, paving the way for the introduction of novel androgen therapies such as abiraterone acetate and enzalutamide. Recent trials on these treatments have demonstrated their benefit to improving overall survival in the setting of mCRPC. The resultant effect is a new, constantly changing, and complex treatment paradigm for treating clinicians, who are now required to know the mechanism of actions of new medications, side effect profiles, modes of administration, and preferred sequencing of various treatment options. Furthermore, treatments involving new androgen biosynthesis are currently being developed and tested. Therefore, in the context of a highly heterogenous disease with a continuously changing treatment landscape, management of mCRPC can be particularly challenging.

The purpose of this review is to provide an overview of the literature on new androgen receptor targeted therapies, and discuss the changing treatment landscape specific to metastatic CRPC.

1. Introduction

Prostate cancer is currently the most frequently diagnosed cancer in men, and the third leading cause of male cancer death, in developed countries.[1] There is an observable increasing trend in the incidence of prostate cancer worldwide, in the context of increasing use of prostate specific antigen (PSA) testing.[2] However, mortality rates for prostate cancer have fallen in developed countries, and this has been attributed to improved treatment and earlier detection.[3]

Prostate cancer that is detected early is usually treated with local therapy, mainly surgery or radiotherapy. Despite this, up to thirty percent of men in Taiwan have metastatic prostate cancer at the time of diagnosis,[4] and approximately half of metastatic prostate cancers progress to castration resistant disease within two years of follow-up.[5] Metastatic castrate resistant prostate cancer (mCRPC) is broadly defined as disease progression despite established androgen depletion therapy; signs and symptoms of progression include sequential PSA rises, progression of pre-existing disease, and/or the appearance of new metastases evident on imaging (CT, MRI or radionuclide bone scintigraphy).[6]

Androgen deprivation therapy (ADT) underpins the treatment approach to metastatic hormone sensitive prostate cancer.[7] This involves suppressing circulating testosterone to an undetectable level leading to a reduction in cancer cell proliferation and/or cell

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death. Standard approaches to ADT can be divided into surgical – bilateral orchidectomy – and medical using a luteinising hormone-releasing hormone (LHRH) analogues alone or in combination with an androgen receptor (AR) antagonist. Although initial responses to ADT are favourable, disease progression to mCRPC, defined by its resistance to traditional hormonal therapies, is common.[5,8,9]

ADT for mCRPC has been an area of focus in recent years in the light of new research that has improved our understanding of the molecular mechanisms behind mCRPC and the androgen receptor as a target. A number of Phase III trials demonstrating improvement in overall survival and progression-free survival has led to the introduction of novel androgen therapies such as abiraterone acetate and enzalutamide.[10,11] This has resulted in a more complicated paradigm for clinicians, with the 'jobbing' oncologist or urologist now required to know the mechanism of actions of new medications, side effect profiles, modes of administration, and preferred sequencing of various treatment options. Indeed, the heterogeneity of mCRPC and consequent permutations of clinical scenarios make management particularly challenging.

The purpose of this review is to provide an overview of the literature on new androgen receptor targeted therapies, and discuss the changing treatment landscape specific to mCRPC.

2. AR as a therapeutic target for CRPC

The AR is a transcription factor that plays a key role in normal prostate cell growth. There is increasing evidence that androgen receptor activity persists in almost all patients who develop castration-resistant disease, and is thus a valid drug target for all stages of prostate cancer.[5,12] After treatment by medical or surgical castration, prostate cancers adapt to the androgen-deprived environment to maximise androgen receptor function through mechanisms facilitated by the genetic instability of cancer cells.[5,13] These mutations in the androgen receptor gene give "new" receptor functionality by allowing the androgen receptor to be activated by ligands other than testosterone or dihydrotestosterone, such as hydrocortisone and progesterone.[14,15]

3. Literature search

We searched each of PubMed, MEDLINE and EMBASE from January 2000 to January 2017 using combinations of the following key words: "prostate cancer", "androgen deprivation therapy", "castrate resistant", "androgen independent", "anti-androgen", "androgen receptor", "androgen receptor targeted therapy", "androgen receptor blocker", "androgen receptor signalling", "androgen receptor signaling inhibitor", "androgen synthesis inhibitor", "abiraterone", and "enzalutamide". Peer-reviewed articles from retrospective reviews, high quality systematic reviews and meta-analyses were included. Only full-text, English language and peer-reviewed publications were included.

4. Treatment options for metastatic castration-resistant disease

Treatment for mCRPC aims to 'control' rather than 'cure' the disease. Prior to the introduction of novel androgen receptor targeted therapies, chemotherapy was the mainstay of treatment for mCRPC. Chemotherapy acts to interrupt cell division (mitosis), which results in decreased cancer cell proliferation. Those most commonly used in prostate cancer (taxanes) do this by inhibiting microtubule disassembly, an important step in chromosomal replication during the M phase of the cell-cycle. Docetaxel was shown in Phase III trials in 2004 to improve overall survival and became the standard second-line therapy (after androgen blockade) in conjunction with prednisone.[8,16] Newer chemotherapeutic agents such as cabazitaxel have since been introduced and have been shown to improve overall survival in patients previously treated with docetaxel.[17,18] Other treatment options for mCRPC include immunotherapies such as Sipuleucel-T for asymptomatic or minimally symptomatic mCRPC,[19,20] and radionuclide therapies (e.g. Radium-223, strontium, samarium).[21] The uptake of these last two options has been limited by cost.

Androgen receptor antagonists and androgen synthesis inhibitors are the mainstay of androgen receptor targeted therapies. The first generation AR antagonist was flutamide followed by second-generation bicalutamide and nilutamide. Bicalutamide, a derivative of flutamide, remains the most commonly used AR antagonist, but more recent attention has focussed on third-generation AR antagonist enzalutamide. First and second-generation AR antagonists, though developed to inhibit AR function, were later found to provide incomplete inhibition due to partial or weak AR co-activator and agonist actions.[22] Bicalutamide is usually administered at 50 mg daily, with studies having shown similar responses with this lower dose when compared to higher doses of 200 mg daily and 150 mg daily.[23–25] Mixed efficacy has been shown for nilutamide as a second-line agent for patients who failed treatment with bicalutamide or flutamide.[26,27] Anti-androgen withdrawal syndrome, the sudden clinical improvement and decline in PSA on withdrawal of hormone treatment in hormone resistant prostate cancer, has been shown to occur in a subset of patients (15–30%) and can last up to six months; withdrawal responses have been reported in bicalutamide, nilutamide and flutamide.[28,29]

Historically, anti-androgen therapies focussed on the use of LHRH agonists, with or without the addition of an AR antagonist such as bicalutamide. LHRH analogues work on the principle of negative feedback. There is an initial flare in serum testosterone in response to the increase in LHRH levels, prior to negative regulation leading to suppression of GnRH release from the hypothalamus and consequent reduction in LHRH and testosterone levels. AR antagonists are usually offered prior to starting LHRH treatment to mitigate the initial testosterone spike and continued for approximately two weeks after commencement of LHRH therapy to cover the flare period.[30]

Abiraterone and enzalutamide, the most recently licenced hormone agents, are discussed in greater detail below. Both have been approved as oral agents for mCRPC having been shown to improve overall survival in men with disease progression after docetaxel. Table 1 provides a summary of the mechanism of actions, side effect profiles, and modes of administration.

4.1. Novel androgen receptor antagonist

4.1.1. Enzalutamide

Enzalutamide (MDV-3100) is an androgen receptor signalling inhibitor (ARSI) that binds the androgen receptor ligand binding domain (LBD) and thereby inhibits nuclear translocation of the androgen receptor, thus inhibiting the association of the androgen receptor with nuclear DNA.[31,32] It was discovered by laboratory driven research in New York and is a fine example of bench to bedside science.[33]

A large phase III trial, the AFFIRM study, compared enzalutamide with placebo in men with mCRPC previously treated with docetaxel.[34,35] In this study, overall survival was significantly greater with enzalutamide compared with placebo (median 18.4 vs 13.6 months, HR 0.63, 95% CI 0.53–0.75; $p < 0.001$). Furthermore, enzalutamide demonstrated significant benefit across all study secondary endpoints of this study. These included a greater than 50% decrease in PSA (54% vs 2%; $p < 0.001$), a greater than 90%