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Urologic Oncology: Seminars and Original Investigations 33 (2015) 310–321

UROLOGIC ONCOLOGY

Review article

Battling resistance mechanisms in antihormonal prostate cancer treatment: Novel agents and combinations

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Received 30 September 2014; received in revised form 11 January 2015; accepted 12 January 2015

Abstract

Prostate cancer (PCa) is a hormone-sensitive disease. Androgen deprivation therapy lowers serum testosterone levels (castration) or blocks the androgen receptor (AR) ligand-binding domain. Especially in metastatic disease, hormonal therapy has been able to delay disease progression, reduce symptoms, and improve overall survival. Despite subsequent disease progression and development of castration resistance, PCa remains AR driven. Secondary hormonal treatments such as abiraterone acetate or enzalutamide have demonstrated increased overall survival. However, new resistance mechanisms to these agents have been identified, and systemic chemotherapy is still needed especially in fast-progressing castration-resistant PCa. Several promising androgen synthesis inhibitors (orteronel and galeterone), AR inhibitors (ARN-509, EPI-001, AZD3514, and ODM-201), and heat shock protein modulators (AT11387, 17-DMAG, STA-9090, and OGX-427) are currently under investigation. The wide variety in upcoming systemic agents underlines the molecular heterogeneity of castration-resistant PCa. This article reviews antihormonal therapy in PCa and resistance mechanisms and focuses on novel and upcoming agents currently in clinical testing.

Keywords: Abiraterone; Antiandrogens; Drug resistance; Enzalutamide; Prostatic neoplasms; Castration resistant

1. Introduction

In an aging population, prostate cancer (PCa) has become the most common malignancy reported in men, and it is the third most common cause of cancer-related death in Europe [1,2]. The introduction of serum prostate-specific antigen (PSA) level measurement has increased PCa detection with a stage migration toward more localized and more low-grade tumors [3]. Regardless of type of early treatment, 20% to 30% of patients experience cancer recurrence or present with multiple metastases at diagnosis. These patients require systemic therapy, starting with androgen deprivation therapy (ADT), which targets the androgen receptor (AR) pathway [4]. Eventually, PCa progresses to castration-resistant PCa (CRPC), and other treatment modalities (secondary hormonal interventions or chemotherapy) are initiated. This article focuses on novel AR-targeted therapies (recently approved or in clinical studies) tackling resistance mechanisms, introducing a modern targeted treatment model for advanced PCa.

2. Methods

Upcoming agents in PCa were searched using a pubmed.gov search (Details: (“prostatic neoplasms”[MeSH Terms] OR (“prostatic”[All Fields] AND “neoplasms”[All Fields]) OR “prostatic neoplasms”[All Fields] OR (“prostate”[All Fields] AND “cancer”[All Fields]) OR “prostate cancer” [All Fields]) AND novel [All Fields] AND agent [All Fields]). This search was restricted to a publication date within the past 5 years. Active clinical studies using the agents of interest were searched using the http://clinicaltrials.gov, https://www.clinicaltrialsregister.eu/, and http://www.controlled-trials.com/isrctn websites up to August

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http://dx.doi.org/10.1016/j.urolonc.2015.01.008
1078-1439/

2013. Agents without active phase I, II, or III trials were excluded from this review.

3. The AR pathway and ADT

The AR plays a central role in PCa development and progression (Fig. 1). The AR gene is located at chromosome X locus q11–12 [5]. The length of the AR gene coded protein is variable, and some evidence points to a higher risk of PCa in men with shorter (more active) AR [6]. The AR is composed of a COOH-terminal ligand-binding domain (LBD), a DNA-binding domain, a hinge region, and a NH_2-terminal domain (NTD) [7]. The cytoplasmic steroid receptor is stabilized by 2 chaperone heat shock proteins (HSPs). The androgens testosterone and the more potent dihydrotestosterone bind the AR LBD inducing a conformational change through which the AR loses its chaperones, dimerizes, and translocates to the nucleus. The AR dimer binds AR-responsive elements in the DNA and interacts with more than 150 different coregulators to initiate transcription, which induces cell growth, proliferation, and PSA secretion [8].

Testicular testosterone production is regulated by the hypothalamic-pituitary axis. The hypothalamus secretes luteinizing hormone (LH)–releasing hormone (LHRH), which stimulates the pituitary gland to produce LH, which in turn stimulates the Leydig cells for testosterone production. In the prostate cell, testosterone is converted into dihydrotestosterone by the enzyme 5α-reductase.

In PCa, the AR pathway is attacked by either lowering ligand concentration or blocking the AR LBD.

3.1. Androgen synthesis inhibition

ADT was first described by Huggins [9] in 1942. By current standards, serum testosterone levels can be lowered <50 ng/dl by surgical (bilateral intratunical orchiectomy) or chemical castration. LHRH agonists (goserelin, histrelin, leuprolide, and triptorelin) cause a burst in LH secretion in the pituitary gland and increased testosterone production in the testicular Leydig cells (flare phenomenon). Persistent LHRH stimulation causes a down-regulation of LHRH receptors and a drop in testosterone to castrate levels. In contrast, the LHRH antagonist degarelix does not cause testosterone flare and demonstrates longer time to PSA level progression in patients with metastasis with a pretreatment PSA level >20 ng/ml compared with LHRH agonists [10,11]. In the past, estrogen therapy (mostly diethylstilbestrol) was applied to induce castration, but this has largely been abandoned owing to an elevated cardiovascular risk [12]. ADT is indicated concomitantly with curative radiotherapy, ranging from 6 months (intermediate-risk PCa) to 2 to 3 years (high-risk PCa), and is the first-line therapy in metastatic PCa [4].

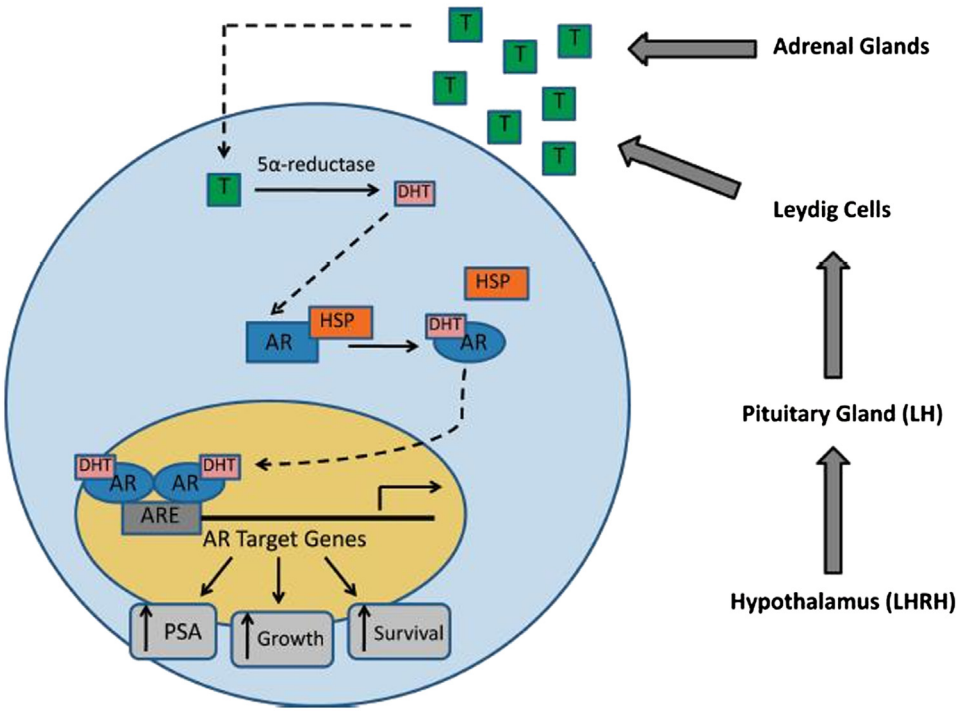

Fig. 1. Androgen receptor pathway. The hypothalamic-pituitary axis drives the testicular Leydig cells to produce testosterone (T), which enters the prostate cell and is converted to the more potent dihydrotestosterone (DHT). Additionally, androgens are produced in the adrenal glands. Androgen receptor (AR)-DHT binding induces a conformational change in the AR, which loses its chaperone heat shock proteins (HSP), dimerizes, and translocates to the nucleus. There it binds androgen-responsive elements (ARE) in the DNA and initiates cellular growth, proliferation, and prostate-specific antigen (PSA) secretion. (Reprinted from Saraon et al. [8].) (Color version of figure is available online.)