Cancer Treatment Reviews 48 (2016) 25–33

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Tumour Review

A comprehensive review of genomic landscape, biomarkers and treatment sequencing in castration-resistant prostate cancer

Thomas Seisen [a,b], Morgan Rouprêt [a,b,*], Florie Gomez [c], Gabriel G. Malouf [d], Shahrokh F. Shariat [e], Benoit Peyronnet [f], Jean-Philippe Spano [d], Géraldine Cancel-Tassin [b], Olivier Cussenot [b,g]

[a] Academic Department of Urology of La Pitié-Salpétrière, Assistance-Publique Hôpitaux de Paris, Faculté de Médecine Pierre et Marie Curie, University Paris 6, 75013 Paris, France
[b] Institut Universitaire de Cancérologie, Pierre et Marie Curie, University Paris 6, GRC n° 5, CeRePP/ONCOTYPE-URO, 75013 Paris, France
[c] Department of Urology, CHC Liege, Liège, Belgium
[d] Academic Department of Medical Oncology of La Pitié-Salpétrière, Assistance-Publique Hôpitaux de Paris, Faculté de Médecine Pierre et Marie Curie, University Paris 6, GRC n° 5, ONCOTYPE-URO, 75013 Paris, France
[e] Academic Department of Urology and Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Vienna, Austria
[f] Academic Department of Urology, CHU Rennes and University of Rennes, France
[g] Academic Department of Urology of Tenon, Assistance-Publique Hôpitaux de Paris, Faculté de Médecine Pierre et Marie Curie, University Paris 6, 75013 Paris, France

ARTICLE INFO

Article history:
Received 7 March 2016
Received in revised form 2 June 2016
Accepted 6 June 2016

Keywords:
Prostate neoplasms
Castration-resistant
Biomarkers
Receptors
Androgen
Genetic
Abiraterone acetate
MDV 3100
Docetaxel
Cabazitaxel

ABSTRACT

Hormone-naïve prostate cancer and its castration-resistant state (CRPC) are clinically and genetically heterogeneous diseases. From initiation of prostate carcinogenesis to its evolution towards therapeutic resistance, various combinations of genetic and epigenetic events occur. Schematically, progression to CRPC could be divided in two distinct pathways, either dependent or independent of the androgen receptor activity. Nevertheless, because the better knowledge of the genetic landscape of CRPC is under way, limited clinical applications are available at the moment, underlying the usefulness of prognostic and predictive biomarkers in daily practice. Despite the promising prognostic value of circulating tumor cells, no biomarker has been currently validated as a surrogate for overall survival in CRPC patients. Inversely, considerable interest has been generated with the recent finding of the splice variant AR-V7 that allows to predict resistance to abiraterone acetate and enzalutamide. However, other predictive biomarkers would be necessary to accurately guide personalized sequencing of CRPC treatment, which now includes numerous possibilities based on the six validated drugs, without accounting for those currently under investigation in the ongoing randomized controlled trials. As a consequence, only rational sequencing, which consists in choosing an agent that is not expected to have cross-resistance with previous therapy, can be currently advised.

Introduction

Hormone-naïve prostate cancer (HNPC) and its castration-resistant state (CRPC) are clinically and genetically heterogeneous diseases [1]. It is now well-established that some patients diagnosed with metastatic HNPC will rapidly progress to the lethal CRPC phenotype while others will show long-term and durable response to androgen deprivation therapy. Preliminary reports suggest that such a transition from HNPC to CRPC might be driven by a wide range of genetic events leading to distinct progression pathways either dependent or independent of the androgen receptor (AR) activity [1–4].

Because of the greater understanding of CRPC biology, docetaxel (DCT) based treatment landscape has dramatically changed over last years. New systemic therapies, including the androgen biosynthesis inhibitor abiraterone acetate (AA) [5,6] and the next-generation androgen receptor antagonist enzalutamide (ENZ) [7,8] have demonstrated to prolong overall survival (OS) in both post- and, more recently, pre-DCT settings (Fig. 1). Along with AA and ENZ, the bone targeted agent alpha emitter radium 223 [9] and the immunotherapeutic sipuleucel-T [10] are also effective treatment options for the management of chemotherapy-naïve patients while the taxoid cabazitaxel (CZT) [11] remains the standard of care for those pretreated with DCT. Sequencing all these innovative agents according to individual characteristics is now the challenge that physicians face in daily practice. Interestingly, there is intensive research to develop prognostic and predictive biomarkers for guiding clinical decision making and achieve

* Corresponding author at: Academic Urology Department, Hôpital Pitié, 47-83 bvd de l'Hôpital, 75013 Paris, France.
E-mail address: morgan.roupret@aphp.fr (M. Rouprêt).

http://dx.doi.org/10.1016/j.ctrv.2016.06.005
0305-7372/

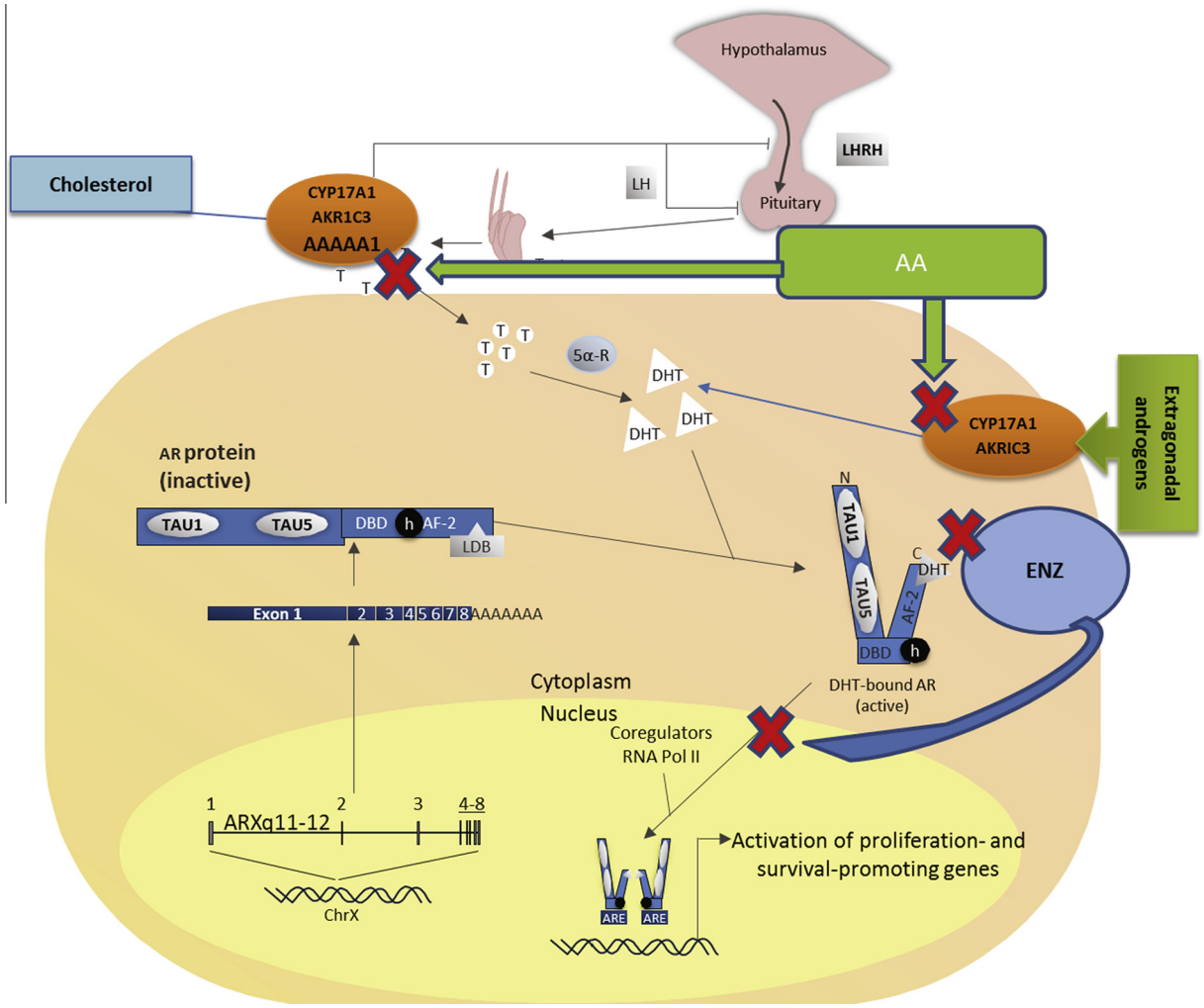

Fig. 1. Androgens receptor axis and action sites of news hormonal agents in CRPC. Adapted from Kohli et al. [12].

optimal medical management of CRPC [12,13]. Therefore, our purpose was to describe the current knowledge of CRPC genomic landscape and to summarize the established and potential biomarkers as well as available evidence for treatment sequencing of patients diagnosed with metastatic disease.

From HNPC to CRPC

Genetic landscape of HNPC

The earliest molecular events commonly reported in human prostate carcinogenesis are the loss of 8p21 region including NKX3 locus, the CpG island promoter methylation of GSTP1 gene, and particularly, androgen driven gene fusions (ETS positive) such as TMPRSS2-ERG fusion gene [14]. Through this ETS positive pathway, deletions at 10q24 region including PTEN locus and gains at 8q24 region including cMyc locus have been shown to foster further disease progression [14].

Alternatively, mutations of the SPOP gene have been recently identified as a key genomic event involved in the natural history of HNPC without any androgen driven gene fusions [14]. Indeed, these mutations result in the inability of the tumor cells to bind and promote the degradation of SRC-3, leading to increased androgen signaling. Through this ETS negative pathway, further disease progression might be induced by the deletion or the silencing of CDH1 gene [14]. More evidence to support distinct ETS positive and negative pathways has been recently reported by Grasso et al. who demonstrated that deregulations of ETS2 were specifically involved in growth of tumors with TMPRSS2-ERG fusion gene whereas disruptions of CDH1 might define a subtype of fusion gene free tumors (Fig. 2) [2].

Chromoplexy and chromotripsis models

From initiation of HNPC to its progression towards therapeutic resistance and death, various combinations of genetic and epigenetic events occur (Figs. 3A and 3B). Next generation sequencing of prostate cancer prior to and following androgen deprivation therapy has dramatically helped to identify important androgen-regulated pathways or genes that may be reactivated in CRPC [15]. Specifically, chromosomal rearrangements, amplifications, deletions, or point mutations and DNA methylation alterations allow for emerging aggressive clones [16]. These mechanisms involved in progression to the lethal stages are usually described according to the chromoplexy model, which drives the punctuated progression of HNPC and induces the formation of disrupted cancer genes such as ERG fusion with TMPRSS2, NKX3-1, TP53, RB1, CDKN13 and PTEN [17]. Alternatively, the chromotripsis model, based on high genetic instability with numerous chromosomal rearrangements and hypermutational status, has been proposed to explain the catastrophe scenario related to terrible disease